Division of Research Resources Annual Report Fiscal Year 1984

(October 1, 1983—September 30, 1984)

National Institutes of Health
Bethesda, MD 20205

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TABLE OF CONTENTS

Report of the Director

In Fiscal Year 1984, the budget of the Division of Research Resources (DRR) of the National Institutes of Health (NIH) was $243,177,000, from which the Division made extramural awards which totaled $236,324,506. This allowed DRR to meet its program commitments and to continue its support of 166 major shared research resource centers throughout the United States.

The DRR awarded 965 research grants, 13 research training grants, and 3 research contracts in support of general clinical research centers (GCRC's), biomedical research technology resources, animal resources, minority biomedical research support, and the biomedical research support program. The number of extramural research grants made from the research resources appropriation increased by 64 (7.1 percent) over 1983, whereas the dollar amount awarded increased by $29,129,000 (14.7 percent).

The DRR budget provided $81 million for support of 75 general clinical research centers; $47.1 million for 546 Biomedical Research Support Grant awards; $19.8 million for 115 Biomedical Research Support Shared Instrumentation Grants; $26.3 million for 47 biomedical research technology resource centers; $28.8 million for 44 laboratory animal science centers and primate research centers, of which $1 million was included for repair and renovation at the primate centers; and $21.8 million for 79 Minority Biomedical Research Support awards. The table following this report provides a breakdown of funding to the DRR's five programs: the General Clinical Research Centers Program, the Biomedical Research Technology Program (formerly called the Biotechnology Resources Program), the Animal Resources Program, the Biomedical Research Support Program, and the Minority Biomedical Research Support Program.

A number of significant personnel changes took place in Fiscal Year 1984. Early in the fiscal year, Dr. William R. DeCesare, Director of the General Clinical Research Centers (GCRC) Program for the past 15 years, died suddenly of a heart attack. A memorial service was held for him in Bethesda with Dr. Charles Hollander, GCRC Program Director and Professor of Medicine at New York University Medical Center, delivering a eulogy. The DRR Deputy Director has acted as Director of the program during the protracted search for a replacement.

In other personnel developments, Mr. Louis Wagner, Grants Management Officer for the Division, retired in early September. He had been a vital part of the DRR Office of Grants and Contracts Management since 1966. Ms. Jeanette Hinde, formerly Grants Management Officer/Deputy Chief, Grants Operation Branch, National Heart, Lung and Blood Institute (NHLBI), was named Grants Management Officer at the close of the fiscal year.

The Committee Management/Council Assistant, Ms. Lilien Wohl retired late in the fiscal year and was replaced by Ms. Kathleen Thomas.

Dr. William R. Baker, Jr., health scientist administrator with the Biomedical Research Technology Program, retired in January 1984. Dr. Baker had been a key mover in the development of artificial intelligence in medicine and was involved in the development of CLINFO, a simplified data analysis system for clinical investigators, since the inception of the system by the Division in 1972. The search for his replacement is underway.

During the past year, staffing of the Division's Office of Review was completed with the addition of Dr. Ai-Lien Wu. Dr. Wu, a graduate of the NIH Grants Associates Program, shares responsibility with the Executive Secretary of the Minority Biomedical Research Support Subcommittee of the General Research Support Review Committee, Dr. Ethel Jackson, for review of the Minority Biomedical Research Support Grant applications.

By the end of Fiscal Year 1984, a total of 38 CLINFO sites had been established, serving 46 of the 75 GCRC's. An electronic mailnet, which the CLINFO II advisory committee recommended, was initiated on an experimental basis, first between Duke University and the University of Cincinnati, and then extended to six additional CLINFO sites. The trial is continuing, with an eye to more widespread application, should the results warrant.

During the past year, assessments of the condition of physical facilities, made at all seven of the now 25-year-old primate research centers, revealed need for extensive plant renovations and repairs, and for replacement of major equipment items. A special Congressional earmark in Fiscal Year 1984 enabled DRR to begin to address these important needs at centers. The funds ($1 million) have allowed some of the centers' highest priority repair and renovation requirements to be met.

The breeding of endangered and scarce primate species at the primate centers continued during the year. Although this effort often represents a burden on scarce resources, it is worthwhile because the number of primate species available in the world is shrinking rapidly because of habitat loss to agriculture.

An evaluation, conducted under contract with the National Academy of Sciences (NAS), was begun on the relevance and limitations of the use of cell systems, lower organisms, and nonbiological systems as models in biomedical research. If the results of the study indicate a need, an extramural grants program in Biomedical Research Model Development will be initiated.

An evaluation of the Biomedical Research Support Grant (BRSG) Program was conducted in Fiscal Year 1984. Among the conclusions of the study were:

that the BRSG Program funds were reaching the institutional programs, departments, and investigators for which they were intended, and, as far as the study could determine, were resulting in impressive benefits; that the BRSG funds were highly valued by both investigators and administrators because of their flexibility and the institution's ability to administer them on a quick turn-around basis.

Fiscal Year 1984 marked the third year of operation for the BRSG Shared Instrumentation Grant Program. From its beginning in 1982, support for the program has grown steadily, from $3.7 million to $19.7 million in Fiscal Year 1984. Because of budget increases, the number of awards for large-scale instrumentation shared among individuals, research groups, departments, and institutions expanded from 23 in 1982 to 115 in 1984.

Plans for the future of the Biomedical Research Technology Program PROPHET Computer Resource were developed during the year. A PROPHET Advisory Panel was assembled to provide the Program advice on future directions for PROPHET. As a result of the Panel's recommendations, a Request for Proposal (RFP) for redevelopment of PROPHET's software and hardware was issued; a contract for PROPHET II, the second generation network, is expected to be awarded during Fiscal Year 1985.

About 1,500 student and faculty participants in the Minority Biomedical Research Support Program gathered in Washington, D.C., in mid-April for the 12th Annual MBRS Symposium. The students presented 570 papers and poster displays. Both faculty and students engaged in workshops on electron microscopy and high-performance liquid chromatography. Mini-symposia and lectures on "Nutrition and Aging," "Hypertension," and "AIDS" also were attended by interested students and faculty.

Based on extensive consultation, including the Fiscal Year 1983 NARRC-sponsored retreat, the Minority Biomedical Research Support Program developed two more initiatives for 1985 during the year. One initiative focused on biomedical research participation by undergraduate colleges that have substantial enrollments of minority students and are not currently funded by the MBRS Program. The other is designed for minority institutions with more biomedical research faculty and updated research equipment which are capable of developing greater faculty and interdepartmental collaboration around specific research themes or disciplines. This "Thematic Project Grant," a new type of MBRS award, is planned as another transitional step toward regular NIH grant support.

Three meetings of the National Advisory Research Resources Council took place during the year with major presentations on the Biomedical Research Technology Program, Technology Assessment at NIH, and DRR Budgetary Trends. Regular meetings of the DRR's research review/advisory committees (GCRC, BRTP, BRSG, and MBRS) took place along with the workshops on special topics including the PROPHET "Colloquium," MBRS Grantsmanship Workshop, Future

Directions in Electron Microscopy, and Viral Infections of Laboratory Rodents. In addition, meetings were held by Program Directors of several of the programs, including the GCRC Program Directors, the MBRS Program Directors, and the Primate Research Center Directors. The DRR Director participated in most of these activities.

Among significant communications activities for Fiscal Year 1984, the Division's Office of Science and Health Reports planned, coordinated, and participated in eight special events, including General Clinical Research Center 20th anniversary celebrations, press briefings, and dedications. The DRR Director participated in most of these events, presenting a commemorative plaque to the principal investigator on each of these special occasions. Dr. James Wyngaarden, Director of NIH, spoke on "New Challenges in Outpatient Research and Training" at the dedication of the University of Texas Health Science Center, Dallas, GCRC Outpatient Unit. Noted National Institute of Mental Health neurologist Dr. Louis Sokoloff delivered a lecture entitled "Visualization of Brain Function" to dedicate the Laboratory of Neuro Imaging at Washington University, which was funded under the DRR Shared Instrumentation Grant. The National Center for Biomedical Infrared Spectroscopy of Battelle Laboratories, Columbus, Ohio, supported by the Biomedical Research Technology Program, was dedicated by Dr. William F. Raub, NIH Deputy Director for Extramural Research and Training who spoke on "Funding Trends in Biomedical Research." Dr. Doris Merritt, Special Assistant to the NIH Director, spoke on medical training and clinical research at the University of Tennessee Center for the Health Sciences GCRC 20th anniversary celebration. Other GCRC 20th anniversary celebrations were held at the University of California, San Francisco GCRC, and at the Medical College of Wisconsin. A press briefing was held on potassium citrate, an orphan drug present in citrus fruits which is used to treat kidney stones, at the GCRC at the University of Texas Health Science Center, Dallas. Scientists from the University of Washington Medical Center and the Regional Primate Research Center in Seattle held a media briefing on improved cochlear prosthesis that was about to be clinically tested.

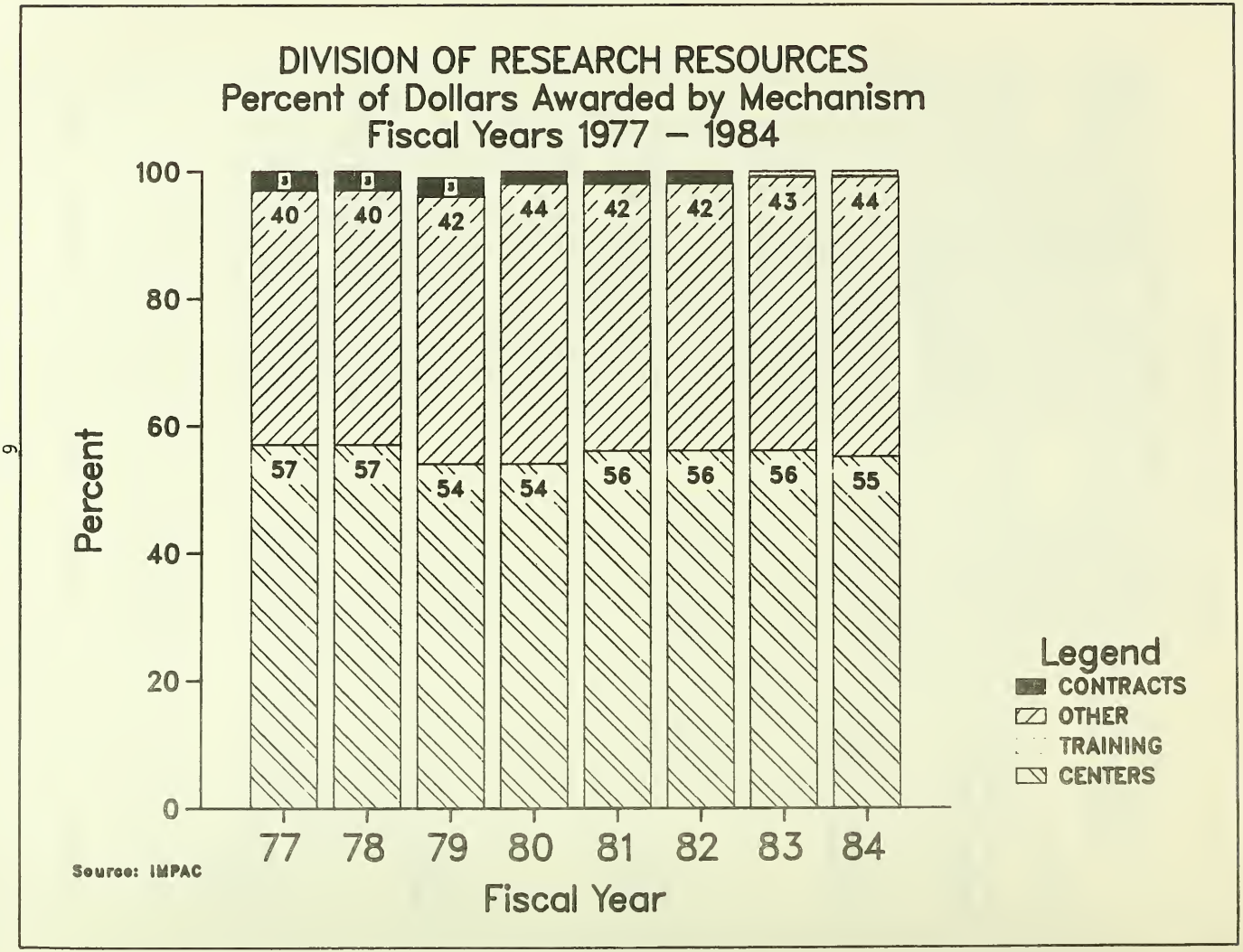
During the year, the Division's publications, produced through its Office of Science and Health Reports and its Research Resources Information Center, won four awards, including the first presentation of the Eric Martin Award for the best article, brochure, or monograph on therapeutics or pharmaceutical services from the American Medical Writers Association. The award went to "Monoclonal Antibodies Against Cancer: Clinical Application" published in the Research Resources Reporter. Other awards came from the Health Sciences Communication Association and the National Association of Government Communicators.

DIVISION OF RESEARCH RESOURCES

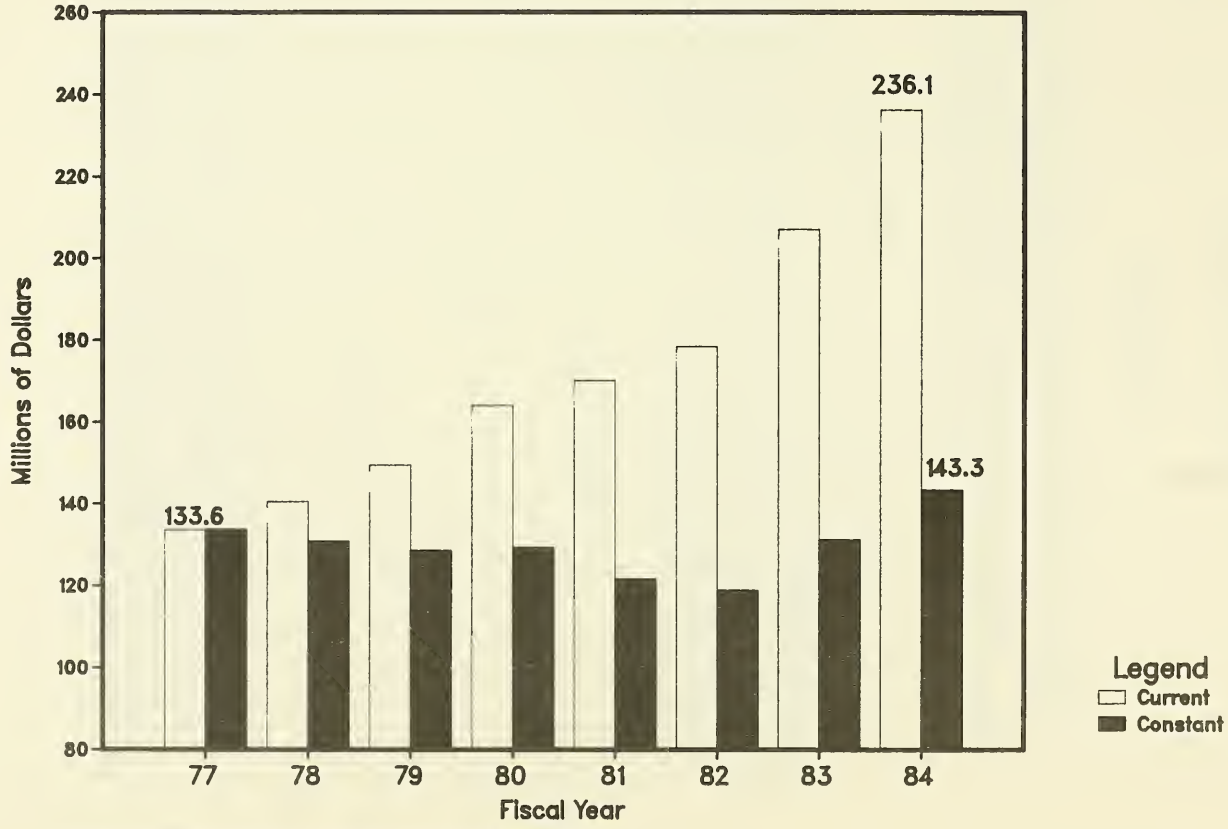
FY 1984 OVERVIEW OF EXTRAMURAL ACTIVITIES

Program	1984 Actual Obligations	Major Resources Supported
General Clinical Research Centers Program	$ 81,679,464	o 75 general clinical research centers o 48 Clinical Associate Physicians o 37 CLINFO awards
Biomedical Research Technology Program	$ 33,434,455	o 47 biomedical research technology resource centers o 3 contracts, including the PROPHET computer network o 13 resource-related research project grants o A small grants program
Animal Resources Program	$ 31,434,588	o 7 primate research centers o 37 animal resource grants o 14 resource-related research project grants o 5 special emphasis research career awards in laboratory animal sciences o 13 research training programs
Biomedical Research Support Program	$ 67,897,000	o Biomedical Research Support Grants awarded to 546 institutions o 115 shared instrumentation awards o Minority High School Research Apprentice Program made 284 awards to support 666 students
Minority Biomedical Research Support Program	$ 21,878,999	o 79 MBRS awards
Total, Extramural	$236,324,506 a/	

a/ Excludes $1,486,272 of reimbursable authority from other Federal agencies


DIVISION OF RESEARCH RESOURCES
Percent of Dollars Awarded by Mechanism
Fiscal Years 1977 – 1984
Percent
100
80
60
40
20
0
3
40
57
3
40
57
3
42
54
44
54
42
56
42
56
43
56
44
55
77
78
79
80
81
82
83
84
Fiscal Year
Legend
CONTRACTS
OTHER
TRAINING
CENTERS
Source: IMPAC

DRR APPROPRIATION: CURRENT DOLLARS vs. CONSTANT DOLLARS
Division of Research Resources



Fiscal Year Biomedical R & D Price Index (FY 1977 Base)

INTRODUCTION

The goal of the Animal Resources Program is to support resource projects that enable scientists to obtain and use animals effectively in health-related research. Special attention is given to those animal resource activities that support the missions of the various NIH components. The objectives are accomplished through the Regional Primate Research Centers Program and the Laboratory Animal Sciences Program.

REGIONAL PRIMATE RESEARCH CENTERS PROGRAM

NIH initiated the Regional Primate Research Centers Program during the period 1961-1965. The original objective was to meet a recognized need for suitable facilities and appropriate research environments where biomedical research employing the nonhuman primate could be best conducted. Seven regional Primate Research Centers (RPRCs) were constructed, equipped, staffed, and became operational as unique research institutions by 1965. Each center is affiliated with a host academic institution. These centers and their respective locations are:

- University of Washington RPRC, Seattle, Washington
- Oregon RPRC, Beaverton, Oregon
- California RPRC, Davis, California
- Delta RPRC, Covington, Louisiana
- Yerkes RPRC, Atlanta, Georgia
- New England RPRC, Southborough, Massachusetts
- Wisconsin RPRC, Madison, Wisconsin

The centers have resources and research environments suitable for a broad range of biomedical research. The Animal Resources Program provides core operational support for the centers through resource grants. Research projects at the centers are funded largely by NIH categorical Institutes, other Federal agencies, and private foundations, through grants and contracts which are held by core staff and collaborative and/or affiliated scientists. Through their use of nonhuman primate models, these scientists

have made numerous important contributions to biomedical research. During the past year, significant investigations have been carried out in various biomedical areas, including reproductive biology, infectious diseases, behavioral sciences, neurosciences, toxicology, nutritional and metabolic diseases, and environmental health.

In Fiscal Year 1984, Program core support in the amount of $22,361,171 and cofunding in the amount of $213,038 enabled the 135 core staff, doctoral-level scientists, to conduct research in the centers. In addition, the centers' resources and services were made available to 539 affiliated, collaborative, post-doctoral, and visiting scientists from various academic institutions. Research training environments were provided for 178 graduate students engaged in thesis-related research. The Program provided salary support for a total of 763 doctoral-level, technical, and administrative staff personnel.

On a regional basis, the centers provided a total of 4,192 biological specimens to 379 scientists at various research institutions throughout the United States. Scientific productivity within the seven centers has remained very strong during the past year, with 808 journal articles, abstracts, books, and book chapters published by the core staff and affiliated/collaborative scientists. An additional 492 publications of this nature were reported to be pending publication or in press during 1983.

Because of the continuing problems associated with obtaining certain species of nonhuman primates from countries of origin, all seven centers have continued their domestic breeding efforts. The seven centers produced approximately 1,800 live births, embryos, and fetuses in 1983, representing approximately 75 percent of their total primate animal requirements. In addition, they produced 672 live births for primary use in research and testing programs of other Federal agencies, including the Food and Drug Administration, National Aeronautics and Space Administration and the National Institute of Child Health and Human Development. Nuclear colonies of a number of less commonly used primate species have also been maintained to ensure the survival of these species for potential research needs in the future. In 1983, the centers maintained a total of 13,168 primate animals representing 35 species for research and domestic breeding uses.

During the past year, detailed engineering assessments of the condition of physical facilities, now nearly 25 years old, were made at all seven centers. These evaluations revealed the need for extensive physical plant renovations and repairs, as well as the replacement of major equipment items, at a total projected cost of more than $13 million during the period of 1984-88. To begin to address these important needs at all centers, Congress made a special allocation of $1 million for this purpose in Fiscal Year 1984. These funds have allowed some of the centers' highest priority requirements of this nature to be met.

Major research emphasis areas and selected examples of research activities at each center during the past year follow:

CALIFORNIA RPRC, UNIVERSITY OF CALIFORNIA AT DAVIS

The major research areas at the California Regional Primate Research Center relate to environmental health sciences, infectious diseases, perinatal biology and reproduction, behavioral biology, respiratory physiology, and immunology.

Correction of Congenital Hydronephrosis in Utero

Human infants born with advanced congenital hydronephrosis caused by urethral obstruction in utero have severely damaged kidneys, hypoplastic lungs, and musculoskeletal and abdominal wall deformities. Those who survive neonatal pulmonary insufficiency usually develop renal failure. These developmental consequences of fetal urethral obstruction may be averted if the obstruction is relieved early enough in gestation to allow normal development to proceed.

In order to study the pathophysiology of fetal urethral obstruction and the efficacy and feasibility of correction in utero, center investigators have simulated congenital hydronephrosis in fetal lambs and nonhuman primates by surgical means during the last trimester of pregnancy. The fetal rhesus monkey (Macaca mulatta) has been used to assess clinical applicability and technical feasibility and to study the effects of anesthetic and tocolytic agents on uterine contractility and on fetal and maternal well-being. Methods have also been developed to monitor the fetus and mother during and after surgery, refine techniques for fetal exposure and manipulation, and develop techniques for percutaneous sonographically guided placement of Silastic shunts.

To investigate the response of the gravid uterus to anesthetic and tocolytic agents and surgical procedures, 27 pregnant rhesus monkeys from 123-152 days gestation (term, 168 days) underwent implantation of electrodes to monitor uterine electromyographic (EMG) activity. Preterm labor and delivery were induced in 1 of 14 (7.1 percent) monkeys that underwent procedures with minimal uterine manipulation (electrode placement, amniocentesis, and maternal laparotomy); in 3 of 8 (37.5 percent) monkeys that had hysterotomies without fetal surgery; in 9 of 19 (47.7 percent) monkeys that had hysterotomies without fetal surgery; and in 9 of 19 (47.7 percent) monkeys that had hysterotomies with fetal manipulation.

Successful fetal surgery for potentially correctable anatomic abnormalities depends on the control of preterm labor. Continuous monitoring of uterine EMG is a new technique which permits analysis of uterine activity (labor)

and the effects of hysterotomy, fetal surgery, and tocolytic agents on the induction of preterm labor.

These studies may lead to the successful development of techniques which can be used for the early correction of fetal urethral obstruction and its adverse consequences in the developing human fetus. These techniques may also have future applications in the correction of other fetal anatomic abnormalities.

DELTA RPRC, TULANE UNIVERSITY

The Delta Regional Primate Research Center core research programs cover the areas of microbiology and infectious diseases, immunology, parasitology, biochemistry, neurobiology, and urology. The affiliate/collaborative program includes a number of other areas, including vision research.

Experimental Leprosy in Nonhuman Primates

Longitudinal studies were continued on the treated sooty mangabey (Cercocebus atys) with naturally acquired lepromatous leprosy. These investigations have involved two mangabeys that were inoculated with Mycobacterium leprae organisms from the original index case of spontaneous leprosy which was discovered in a mangabey in 1980. In addition, studies were made on two mangabeys that were inoculated with armadillo-passed human M. leprae organisms. All of these animals continued to progress with the lepromatous type of leprosy.

Fourteen additional mangabeys have been inoculated with titrated doses of mangabey-derived M. leprae. Two mangabeys received the organism via aerosol inoculum. Twelve rhesus (M. mulatta) monkeys that received mangabey M. Leprae were also longitudinally studied together with controls. In addition, three squirrel monkeys (Saimiri sciureus) that were inoculated with human M. leprae were closely monitored.

Seven of the most recently inoculated mangabeys (all higher-dose animals) have demonstrated lesions at the inoculation sites five months post-inoculation. Two mangabeys that received the highest dose (approximately 10^{10}) have histopathologic patterns indicative of lepromatous leprosy. The aerosol recipients have not yet shown signs of leprosy. Only one of the inoculated rhesus monkeys has shown clinical signs of lepromatous leprosy, and none of the inoculated squirrel monkeys has developed the disease to date.

In advanced cases of leprosy, mitogen responses and immunoglobulin plaque-forming cell numbers were significantly decreased, while increases in lymphocytes with suppressor cell phenotype were observed. Longitudinal studies of the immunologic parameters since 1980 have revealed that the responsiveness of lymphocytes to mitogens varies on an annual cyclic basis.

This cyclic phenomenon was apparent in both the leprosy-infected and control animals. Cyclic variations (i.e., seasonal fluctuations) in the responsiveness of cells in the immune system could have extremely important implications for an improved understanding of leprosy, as well as other infectious diseases.

The leprosy studies at the Delta Center are being performed in close collaboration with the Yerkes Regional Primate Research Center and the Armed Forces Institute of Pathology. These investigations with nonhuman primate models may contribute significantly to an improved understanding of the basic disease processes involved in human lepromatous leprosy.

NEW ENGLAND RPRC, HARVARD UNIVERSITY

The New England Regional Primate Research Center's core research program covers the areas of microbiology and infectious diseases, psychobiology, comparative pathology, viral oncology, cardivascular physiology, and nutrition. The center's extensive affiliate and collaborative research programs include numerous other biomedical areas of investigation.

Augmentation of Fetal Hemoglobin Production in Anemic Nonhuman Primates

Recent studies at the New England Center have demonstrated that the administration of hydroxyurea, a well-established and safely tolerated chemotherapeutic agent, significantly raises fetal hemoglobin production in anemic, juvenile cynomolgus monkeys (Macaca fasicularis). The mechanism of this action involves the specific toxicity effects of hydroxyurea on the more mature erythroid progenitor cells. This selective toxic effect does not damage the earlier erythroid progenitor cells, which retain the capability for gamma globulin gene expression and then undergo premature terminal differentiation.

After repeated phlebotomies to induce anemia and reticulocytosis in the animals, the administration of hydroxyurea resulted in a dramatic increase in F cells and fetal hemoglobin levels. These responses returned to baseline values after three weeks. These results suggest that the amplification of fetal hemoglobin systems occurs by shifting the origin of reticulocyte production from mature to immature progenitors.

This work has important clinical implications for the treatment of sickle cell anemia, an extremely common and usually lethal disease in the black population. Although fetal hemoglobin does not carry oxygen as well as normal adult hemoglobin, it does so with much more efficiency than sickle hemoglobin. Clinical researchers have long searched for a safe therapeutic

agent that will increase the level of fetal hemoglobin in the blood of patients with this disease. These findings with nonhuman primates led immediately to successful trials of this agent in human patients at Children's Hospital in Boston, Massachusetts. The work has also formed the basis for a collaborative clinical trial of hydroxyurea in sickle cell anemia patients at the Johns Hopkins University Hospital, the National Institutes of Health, and Children's Hospital in Boston.

YERKES RPRC, EMORY UNIVERSITY

Research at the Yerkes Regional Primate Research Center includes psychobiology of great apes and monkeys, anatomical and physiologic aspects of the central nervous system, pathology, reproductive biology, immunology, language acquisition, and development of models for human diseases.

Nonhuman Primate Model for Loss of Visual Acuity and Its Correction

It is believed that near-normal visual acuity can be achieved in eyes compromised by congenital monocular cataracts. In children, early detection and removal of cataracts, followed by prompt correction of the aphakia, is now widely attempted clinically for the treatment of congenital monocular lens opacities.

Newborn rhesus monkeys (Macaca mulatta) underwent lensectomy, as do very young children with cataracts. Following this surgery, which was performed under general anesthesia, the aphakic eye was fitted with a soft, custom-designed, extended-wear contact lens. Ocular measurements of the infant monkeys had been performed preoperatively to facilitate proper fitting of the contact lens. Optimal power of the aphakic lens was calculated from keratometry and axial length measurements and was confirmed by serial retinoscopy. Fluorescein angiogram or angioscopy was performed on each animal to rule out cystoid macular edema.

The loss of visual activity produced by removal of the lens was successfully corrected with the continuous-wear lenses. This work provides a model for study of human infant lensectomy and procedures for the correction of visual losses in children who cannot use eyeglasses or contact lenses which must be removed frequently.

WASHINGTON RPRC, UNIVERSITY OF WASHINGTON AT SEATTLE

The core research program of the University of Washington Regional Primate Research Center includes the areas of neurological sciences, cardiovascular function, developmental biology, disease models, endocrinology and

metabolism, and craniofacial structure and function. An extensive affiliated scientists' program involved more than 60 investigators engaged in a variety of study areas.

Control of Food Intake and Body Weight

Scientists at the center have conducted a study to determine the role of specific peptide hormones in the control of food intake and body weight in baboons (Papio cynocephalus). These investigations were based on the hypothesis that the pancreatic hormone, insulin, acts at the brain level to provide a negative feedback signal which is important in the regulation of food intake and obesity. More insulin is perceived as a higher state of obesity, resulting in a decrease in appetite, and vice versa. After overweight people voluntarily lose weight by dieting, mechanisms within the body eventually tend to restore weight to the original level because of overeating.

It has been known for many years that the amount of insulin secreted from the pancreas is directly proportional to body weight. Obese persons have consistently been found to secrete more insulin than thin persons. However, the amount of insulin found in the blood does not correlate well with body weight.

Previous work at the center showed that the infusion of small amounts of insulin into the lateral cerebral ventricles of baboons causes a dose-dependent reduction of food intake and body weight. These findings led to the examination of interactions of central insulin with other peptides, especially cholecystokinin (CCK), bombesin (BBS), and related analogues, which are believed to cause a reduction in the size of individual meals. It was also known that insulin is present in the cerebrospinal fluid (CSF) of baboons and that it increases as plasma insulin increases (i.e., during meals or after peripheral insulin infusions).

During the past year it was found that the infusion of subthreshold doses of insulin into the CSF increases the sensitivity of baboons to peripheral CCK; i.e., doses of CCK that normally have no effect will reduce meal size by 90 to 100 percent when insulin is infused. Similar experiments with BBS are currently in progress. It was also discovered that the administration of CCK directly into the CSF appears to reduce meal size at lower doses than by its peripheral administration. This is in contrast to findings in most other species of animals. Finally, it was found that the administration of gastrin-releasing peptide (GRP) once every 48 hours at a subthreshold dose (for individual meals) causes a chronic reduction of food intake and a slowing of weight gain.

All of these findings are being actively pursued. It is hoped that new clinical applications can be developed to take advantage of this natural feedback system for the control of body weight in humans.

Focused areas of research at the Wisconsin Regional Primate Research Center include behavioral endocrinology, reproductive physiology, neuroendocrinology, and gonadotropic physiology.

Studies on Fetal Lung Maturation and Respiratory Distress Syndrome in Premature Primate Infants

Scientists at the Wisconsin Center are attempting to identify and fully characterize factors in rhesus monkeys (Macaca mulatta) that delay the maturation of fetal lung and thereby potentially increase the occurrence and/or severity of human respiratory distress syndrome (RDS). The major goals of this project are:

- to define the fundamental features of primate lung development in the normal and diabetic pregnancy;
- to identify factors which alter the lung maturation process;
- to elucidate metabolic abnormalities which increase the susceptibility of infants of diabetic mothers to RDS; and
- to devise and improve methods for prenatal assessment and stimulation of fetal lung maturation for use in pregnant women with diabetes mellitus.

During the past year improvement was achieved in the streptozotocin model of diabetes using infusions of 30 mg/kg. Preliminary data on lung biochemistry indicate that delayed glycogenolysis occurs in fetuses of diabetic pregnancies. Gestational changes in fetal adrenal cortical status have been characterized and correlated with indices of lung development. Fetal lung development has been assessed in multidisciplinary fashion in animals at four gestational ages during the last trimester of control pregnancies. The relationship between fetal sex as a single variable and biochemical and physiological patterns of lung development has been examined and no differences were found between males and females after 135 days of gestation. The complete phospholipid composition of amniotic fluid has been assessed at various gestational ages, revealing that the rise in phosphatidycholine concentration and its ratio to sphingomyelin is a late event in rhesus pregnancies; this change occurs several days after fetal lung maturation is physiologically demonstrable. Furthermore, the appearance of phosphatidylglycerol in amniotic fluid is a very late phenomenon and may not even occur at the termination of gestation when its level in lung has risen substantially. Maternal energy stores and glucoregulation during pregnancy have been analyzed in relationship to fetal growth; attempts to correlate maternal nutritional status with the pattern

of fetal lung maturation are currently underway. Characterization studies on fetal lung collagen content and reducible collagen cross-links are also continuing.

These investigations on the nonhuman primate model are important to gaining an improved understanding of basic factors related to the occurrence of RDS in humans. It is believed that the findings from these studies will contribute to the eventual prevention of this important disease in human premature infants.

OREGON RPRC, OREGON HEALTH SCIENCES UNIVERSITY

Major areas of research emphasis at the Oregon Regional Primate Research Center include reproductive biology, perinatal physiology, immunology, nutrition, toxicology, cardiovascular and metabolic diseases, and behavior.

A Nonhuman Primate Model of Human Gilbert's Syndrome

In their collaborative efforts with scientists at the California Primate Center and the Albert Einstein School of Medicine, investigators at the Oregon Primate Center have established a nonhuman primate model of Gilbert's syndrome. This condition in humans is characterized by increased plasma concentration of bilirubin, a product of erythrocyte removal, and is benign. However, the associated jaundice is frequently confused with liver diseases and other hemolytic conditions.

Previous investigations on bile formation and gallstones in squirrel monkeys at the Oregon Primate Center had demonstrated that Bolivian, but not Brazilian, squirrel monkeys (*Saimiri sciureus*) have fasting bilirubinemia. It was later found that the rate of removal of labeled bilirubin from the blood is delayed in Bolivian squirrel monkeys, which have higher circulating bilirubin levels than Brazilian squirrel monkeys. The Bolivian monkeys were also found to have reduced levels of a key enzyme which is required for bilirubin metabolism in their livers.

Intravenous or intragastric administration of a number of carbohydrates reduced the blood levels of bilirubin in Bolivian squirrel monkeys very rapidly, however, the introduction of lipids (fats) had no effect on bilirubin blood levels. The injection or ingestion of carbohydrates normalized the removal of bilirubin from the blood and increased its excretion into the bile.

These comparisons of normal and abnormal populations of squirrel monkeys as animal models of human Gilbert's syndrome are providing valuable insights into how bilirubin and various other natural and toxic products are removed from the body by the liver.

Simian Acquired Immunodeficiency Syndrome (SAIDS) in the RPRCs

Outbreaks of a spontaneously occurring simian acquired immune deficiency syndrome (SAIDS) have occurred in six different species of macaque monkeys at four of the Regional Primate Research Centers (California, New England, Oregon, and Washington). The epidemiologic, pathologic, immunologic, and virologic features of this disease show many similarities to those seen in human acquired immune deficiency syndrome (AIDS) patients, thus making SAIDS an extremely good model system for basic studies on human AIDS. There is a high mortality rate in nonhuman primates affected by SAIDS, and this disease represents a threat to the health status of thousands of animals in these centers.

Studies to date have resulted in the isolation of type D retroviruses from SAIDS-affected primates at all four centers. At the California Center, the disease has been experimentally transmitted to healthy nonhuman primates by inoculating them with type D retrovirus cultures. These retroviruses, which appear to cause SAIDS, are not the same retroviruses (LAV and HTLV-3) which have recently been isolated and identified as the suspected agents of human AIDS.

Studies on SAIDS at the four RPRCs are continuing. All seven Regional Primate Research Centers are monitoring their nonhuman primate colonies very closely for evidence of SAIDS.

A meeting on SAIDS and other immunodeficiency syndromes was held in Seattle, Washington, May 31 to June 1, 1984. Investigators from the seven Primate Research Centers and their collaborators attended. A previous meeting was held at the Delta Center in December 1983. The participants reported recent findings related to SAIDS in the areas of virology, immunology, epidemiology, pathology, and diagnostic methods at their respective centers. In view of the importance of this disease, a follow-up meeting of center investigators and collaborators working in these areas is planned in early 1985.

Studies on SAIDS at four Regional Primate Research Centers during the past year are summarized below:

CALIFORNIA REGIONAL PRIMATE RESEARCH CENTER

A spontaneous acquired immune deficiency syndrome that is remarkably similar to human AIDS has been under intense investigation at the California Primate Center. The infectious nature of SAIDS has been unequivocally established. The causative agent is presumably a retrovirus similar to Mason-Pfizer monkey virus or a variant thereof. This candidate SAIDS-causing virus has been well characterized, and its disease-producing capability was put to critical test. Investigations are in progress to determine the relationship, if any, of this agent to the putative retrovirus which causes human

AIDS. Identification of the SAIDS virus is only the first step in understanding the pathogenesis of this disease process and in developing effective treatment and preventive measures. This model system will provide, without doubt, an excellent opportunity to understand more fully the interaction of the primate immune system with an apparently "new" family of acquired lymphotropic viruses.

NEW ENGLAND REGIONAL PRIMATE RESEARCH CENTER

Spontaneously occurring rhesus monkey lymphomas were transmitted into healthy rhesus monkeys by using tumor cell suspensions. The naturally arising tumors included an immunoblastic sarcoma and an undifferentiated lymphoma. Recipient animals developed undifferentiated lymphomas, poorly differentiated lymphomas, or parenchymal lymphoproliferative abnormalities suggestive of early lesions of lymphoma. Some of these animals developed such opportunistic infections as cytomegalovirus, hepatitis, and cryptosporidiosis. They also showed evidence of an abnormal circulating peripheral blood mononuclear cell. These findings, all characteristic of the SAIDS of macaques, suggest a link between these transmissible lymphomas and SAIDS in macaque monkeys. SAIDS of macaques was transmitted to previously healthy macaque monkeys by inoculation of either tissue or a cell-free filtrate of a macaque lymphoma. The recipients showed evidence of profound lymphocyte dysfunction or died with infections from such opportunistic agents as Candida albicans, Cryptosporidium, and cytomegalovirus.

Lymph nodes from macaque monkeys with an immunodeficiency syndrome were examined by electron microscopy and both routine histologic and immunoperoxidase staining-techniques, using monoclonal antibodies which recognize specific primate lymphocyte subsets. In the early stages of disease a marked follicular hyperplasia and a reduced paracortex composed predominantly of T8 positive (suppressor/cyotoxic) cells was observed. In monkeys with more advanced disease, lymph nodes showed follicular involution and loss of B cells. Vasculature was seen prominently in the paracortex of these nodes; cellular elements included a mixture of small lymphocytes and larger cells which, by ultrastructural criteria, appeared to be lymphoblasts. Lymph nodes in terminal stages of this disease showed a total effacement of architecture with a marked depletion of lymphocytes. These findings are remarkably similar to the lymph node changes seen in humans with AIDS and underline the importance of this disease in macaques as a model for studying acquired immune deficiency states.

UNIVERSITY OF WASHINGTON REGIONAL PRIMATE RESEARCH CENTER

Since September 1976, the syndrome of retroperitoneal fibromatosis (RF) has been observed in a breeding colony of Macaca nemestrina and occasionally other Macaque species at the University of Washington Center. The tumor arises from the ileocecal junction and initially involves mesenteric lymph nodes. If natural progession is allowed to occur, the tumor will progres-

sively encase the intra-abdominal organs and invade the thoracic cavity. Histologic examination of the affected tissue reveals plump or spindle-shaped fibroblasts in a disorganized stromal network of collagen and reticulum fibers. Diffused and focal infiltration of the fibrous tissue with lymphocytes, plasma cells, and occasional macrophages is common. The morphologic changes in the affected lymph nodes progress from a hyperplastic to a hypoplastic pattern. In the final phase, lymph nodes show both follicular and paracortical depletion and the normal cellular elements are replaced with large histiocytic cells.

Recently, a D type retrovirus was identified and cultured from RF material. Peripheral blood lymphocytes of four Macaca nemestrina with RF were studied for mitogen responses using PHA, Con A, and pokeweed mitogen. Compared with age- and sex-matched controls, all four animals showed markedly depressed lymphoproliferation, especially to the mitogens PHA and Con A (1 to 13 percent of the normal controls). Two Macaca mulatta with RF and two matched controls were immunized intravenously with a T-cell-dependent neoantigen, bacteriophage OX 174. Post-primary and -secondary responses were determined over a ten-week period. The two normal animals showed a typical primary and secondary response, including amplification and switch from IgM to IgG. The RF animals had a markedly depressed primary and a severely suppressed secondary response; they lacked amplification and failed to switch from IgM and IgG antibody. Similar abnormal responses have been observed in human patients who lack T helper cell function.

These studies suggest that RF is associated with a significant immune deficiency affecting both cellular and humoral immunity. It is believed that the D type retrovirus interferes directly with lymphocyte function.

OREGON REGIONAL PRIMATE RESEARCH CENTER

The colony of Celbes apes (Macaca nigra), in which pancreatic amyloidosis and diabetes mellitus are prevalent, has been noted to be in rather poor health for several years. Fertility has been low, infant mortality high, and life expectancy short, although these indicators have not correlated well with diabetic status. Anemia and prolonged, recurrent diarrhea have been obdurate clinical problems. In 1983, these problems were ameliorated, but not eliminated, by single caging of the animals and eradication of endemic intestinal bacterial pathogens, notably Shigella and Campylobacter, by intensive antibiotic therapy.

Acute and chronic inflammatory changes in the intestines have been frequent post-mortem findings in Celebes apes that died spontaneously in the past five years. In many cases, a proliferative, spreading fibrous growth was found in the retroperitoneum and serosa of the bowel.

Some of the Celebes macaques that have been tested showed depressed lymphocyte proliferative responses. Sera from 13 of 46 animals contained anti-

bodies to human T cell leukemia virus, an agent associated with both certain types of human leukemia and human acquired immune deficiency syndrome (AIDS).

Studies of the immunologic properties of lymphocytes in Macaca nigra were extended, because some commercially monoclonal antibodies to human T cell subsets cross-react poorly with T cells from these macaques. Species-specific monoclonal antibodies to T cell subsets have been derived.

In collaboration with the California Regional Primate Research Center, a type D retrovirus has recently been isolated from the tissues of affected Celebes macaques. Studies are continuing to determine the transmissibility of this immunodeficiency syndrome from Celebes macaques to healthy rhesus macaques.

FUTURE DIRECTIONS

The Regional Primate Research Centers will initiate more studies on the epidemiology and pathology of SAIDS. In collaboration among the centers and with interested virologists at NIH and elsewhere, they will work toward developing diagnostic tests for the causative agent, possible immunizing agents, or other control measures. These studies will have direct implications for control of human AIDS.

The centers will continue their efforts to renovate and restore their facilities so that research programs will not be impeded.

The breeding of endangered and scarce primate species will also continue. Although this effort often represents a burden on scarce resources, the spectrum of primate species available in the world is rapidly shrinking because of habitat loss to agriculture, and it is very important to the future of biomedical and behavioral research that some of these species be preserved.

The centers will continue their efforts to provide resources to the interested investigators in the scientific community they serve in their region, and to include more investigators as resources become available.

LABORATORY ANIMAL SCIENCES PROGRAM

The Laboratory Animal Sciences Program (LASP) helps institutions develop and improve animal resources for biomedical research and training through the award of research and resource grants. Program areas include:

- o support for research related to important laboratory animal disease problems;

- o animal colonies which serve as national resources for biomedical research;

- o studies directed at finding animal models which are needed for research on human diseases;

- o institutional animal resource improvement projects to help upgrade animal facilities and develop centralized programs of animal care;

- o laboratories for the diagnosis and control of diseases of laboratory animals; and

- o training of specialists in the field of laboratory animal medicine.

In Fiscal Year 1984, the Program awarded funds totaling $8,978,197, which supported 67 research or resource grants, 10 institutional training programs, and 3 individual fellowship awards.

RESOURCE-RELATED RESEARCH

Animal Disease Problems

Resource-related research grants are awarded to improve the health and availability of research animals and to provide needed information to manage animal resources effectively. The majority of these projects involve investigation of the etiology, pathogenesis, and control of laboratory animal disease problems. For example, current projects include:

- o diagnosis and control of mammalian encephalitozoonosis;

- o control of respiratory mycoplasmosis in rodents;

- o development of a live vaccine for the control of pasteurellosis in rabbits;

- o establishment of resistance and susceptibility factors to Sendai virus infection in mice; and

- o development of a technique for the rapid diagnosis of Herpesvirus simiae (B-virus) infection.

The last project is of particular significance, because of the difficulty of differentiating among a number of herpesvirus infections and the potential for fatal human infection with B-virus from apparently normal rhesus monkeys. Cross-species infection associated with enhanced virulence and a high number of fatalities has also been reported in several nonhuman primate species (owl monkeys, marmosets, and gibbon apes). During the first year of

work on this project, monospecific antisera were used to characterize type-common and type-specific polypeptides and glycoproteins of B-virus with HSV-1, HSV-2, and SA8. Current evidence indicates that B-virus and SA8 probably represent simian analogues of the human herpesvirus HSV-1. The extent of the relatedness and presence of type-specific determinants need to be defined fully. A future goal is to use type-common neutralizing determinants as a safe and effective vaccine.

Population and Breeding

In addition to disease-related studies, several projects involve population studies and breeding of nonhuman primates. Census work and demographic studies of rhesus monkey populations in northern India are nearing 25 years of continuous documentation. The study population increased 18.2 percent during the past year as a result of both high natality (birth rate higher than 90 percent) and low mortality. Infant mortality was exceptionally low--only 1.03 percent (compared to a typical range of 5 to 8 percent).

Juvenile mortality for the entire year was also lower than average at 17.6 percent (compared to a typical range of 30 to 40 percent), and adult mortality was 10.5 percent for the entire year (compared to a typical range of 13 to 17 percent). These favorable demographics were attributed to moderate weather, good agricultural production, and the lack of trapping. The first new natural group formation since 1961 was noted.

Combined with other evidence, it now appears that the effect of the ban on commercial trapping for export, plus favorable weather and generally good agricultural production, are aiding rhesus populations in India. Although it will be a long time before the numbers begin to approach their former level of abundance, the population has grown so rapidly that the rhesus may become a pest problem in some localities. The field trial of subgroup relocation undertaken in 1983 was successful, and a new group of rhesus monkeys has been established in a suitable habitat from which former populations had been eradicated. It was necessary to provision the group longer than anticipated (six months), and the total cost was three times higher than budgeted. After moving about for the first three months, the relocated group picked a specific area as its home range and has remained in a consistent and well-established pattern of behavioral adaptation. This demonstrates that this procedure can be done successfully in an agricultural area with both Governmental and local village acceptance.

Small Business Innovation Research

A new focus of research activity was initiated last year under provisions of the Small Business Innovation Research Development Act of 1982 (Public Law 97-219). This amendment to the Small Business Act required Public Health Service agencies to set aside a specified amount of their research and development (R&D) budgets for a Small Business Innovation Research (SBIR)

Program. The legislation is intended to stimulate technological innovation, use small businesses to meet Federal R&D needs, increase private-sector commercialization of innovations derived from Federal research and development, and foster and encourage participation by minority and disadvantaged persons in technological innovation. The SBIR Program consists of three phases:

- Phase one--the technical merit and feasibility of R&D ideas are established.

- Phase two--the proposed R&D ideas that are likely to result in commercial products or services are developed in detail.

- Phase three--private capital is obtained, where appropriate, to commercialize the results of the R&D.

In Fiscal Year 1984, the Animal Resources Program considered five new SBIR proposals. Of the five, one was approved and subsequently transferred to another Institute for funding. Two hold-over projects from the previous fiscal year were funded ($102,368). The funded projects involve the culturing of amphibians for biomedical research and the development of a microcomputer-assisted data management system for animal resources. The latter project will encompass data associated with investigator use of experimental animals, animal acquisition and disposition, clinical veterinary medical activities, diagnostic and animal health surveillance, facilities management, review of animal-use protocols, inventory control, and fiscal procedures. After completion of the global system conceptual design, the project will focus on design, documentation, programming, testing, and implementation of specific subsystems for the above areas.

The LASP increased its support in the resource-related research area from 13 projects ($965,701) in Fiscal Year 1983 to 19 projects ($1,619,672) in Fiscal Year 1984. There is growing recognition that naturally occurring laboratory animal diseases and environmental factors can have a significant effect on research projects. This year, nine new projects were awarded, including four disease-related studies. The first will study the pathogenesis of mouse hepatitis virus in laboratory mice, the second will examine the responses of inbred mice to ectromelia virus, the third will evaluate a vaccine for the prevention of pasteurellosis in rabbits, and the fourth will study campylobacteriosis in several laboratory species. The latter project is of particular significance, because Campylobacter jejuni has recently been recognized as a common cause of diarrhea in humans, as well as in laboratory animals. A major goal of this project is to evaluate the ferret as an experimental animal model for human infection.

Other new projects funded this year include one to define the major histocompatibility complex of the cynomolgus monkey and a second to develop methods for advancing ovulation and optimizing conception in the dog. The

latter project will evaluate a regimen of repetitive pulses of gonadotropin-releasing hormone, characterize gonadotropin patterns throughout the normal cycle, and evaluate plasma estrogen levels as an indicator of early pregnancy. The development of a simple, effective method of inducing ovulation and shortening the interbirth interval could be particularly important if there are additional restrictions on the use of random source dogs from municipal animal shelters for biomedical research.

ANIMAL MODELS AND SPECIAL COLONIES

The goals of the Animal Models and Special Colonies Program are:

- to define, characterize, and make use of the relevant biological attributes of selected animals which display potential for use in biomedical research; and

- to establish, improve, or expand special colonies of well-characterized animals which are of proven value for biomedical research, but which are not generally available from other sources.

Squid

Animal model projects are conducted using selected species which have potential utility as models in more than one categorical area of research. Several marine invertebrate projects involving octopuses and loliginid squids, for example, are designed to develop a system and methodology for large-scale culture of these species for biomedical research. The usefulness of the squid giant fiber system for neuroscience research is well established. Since 1974, there have been about 35 squid axon papers per year, which represented about 70 percent of all giant axon papers during this period. A second widely used component of the squid giant fiber system is the giant synapse, which lies within the stellate ganglion. The squid synapse has been a particularly good model for studying mechanisms of synaptic transmission at the molecular level. Other components of the squid are equally useful in the research laboratory, including the vertebrate-like eye, statocysts, which are the best-developed organs of equilibrium among invertebrates, and the neurally controlled chromatophores. More than 100 experimental papers have been published on Loligo (not including giant axon papers) in the past two years.

Although the usefulness of the squid for research is well established, the squid's whereabouts and availability are understood far less. The limited numerical and seasonal availability of live squids led to the funding of a Cephalopod Biology Program at the Marine Biomedical Institute, University of Texas Medical Branch, Galveston. The Program has addressed the possibility of establishing new geographic locations for obtaining squids, ways of extending their availability through new or improved capture and maintenance

techniques, and methods to culture squids in the laboratory. Progress to date has been very good. The Program is now providing the small squid, Lolliguncula brevis, year-round. Although its smaller axons are not large enough for voltage clamp and perfusion experiments, this small, hardy species has been used in a variety of studies such areas as osmotic stress, behavior and body patterns, phototransduction, the blood-brain barrier, and nerve regeneration.

Shipboard transport and laboratory maintenance techniques are now well developed and have led to the longest survival of any wild-caught loliginid squid. These refinements have resulted in fewer field collections and transport of live squids to inland laboratories. Culture has been emphasized during the last project period and the squid, Loligo, was cultured through the entire life cycle for the first time. The basic components of a system to culture Loligo have been developed, offering the realistic possibility to provide Loligo of all sizes through laboratory culture. Current experiments with hatchlings of Loligo forbesi are particularly promising, because the axon of this species is large enough for traditional neurophysiologic experiments.

Opossum

Another promising model project involves the development of the short-tailed opossum (Monodelphis domestica) as a laboratory animal. This marsupial, native to Brazil, appears to have many of the attributes that are desirable in establishing a laboratory species; i.e., small size, relative docility, prolific breeding in captivity--gestation period of 14-15 days, reaches sexual maturity in 4-5 months--and relative freedom from disease and parasites. Most of these features are in marked contrast to the severe limitations of working with the Virginia opossum, the North American species most widely used to date. Marsupials are born in a semi-embryonic state, roughly equivalent in development to a rat or mouse at mid-gestation. They have been particularly used for immunologic studies, because they lack thymic lymphoid tissue, peripheral blood lymphocytes, and immunoglobulins at birth. Their low number of large, easily identified chromosomes, neonatal capability of limb regeneration, and simple organization of many cellular and morphologic characteristics make them uniquely suited for many types of biomedical research. The current project aims to establish a suitable dietary regime and appropriate husbandry procedures that will allow efficient production by the colony. During the first two years of the project, more than 2,000 animals have been produced, and the colony now includes 935 adults and juveniles. In comparative dietary studies, fox food "reproduction diet" resulted in significantly faster growth and greater reproduction than three other diets. Four polymorphic genetic markers have been detected, which will aid in determining genetic variation in the colony and development of a strategy of genetic management to maintain that variation.

Special Projects

Special colony projects combine, in varying degrees, the maintenance and production of special strains or stocks of animals with ongoing research to further develop and characterize the models. Currently supported projects include a mouse mutant gene resource at the Jackson Laboratory and development of a set of recombinant inbred (RI) strains of mice at the Salk Institute for Biological Studies. The latter project involves the study of two progenitor strains, plus a derived family of ten RI strains that differ in susceptibility to a large number of pathogens, tumors, autoimmunity, and aging. The strains have all reached the 26th generation of inbreeding and have been sent to laboratories all over the world. There, collaborative mapping studies will examine the genes sites that control 12 different specificities, ranging from expression of immunoglobulins to levels of various enzymes in different tissues. The strains have now been typed for a number of known markers, and by extending this to further alleles, it will be possible to map more complicated phenotypes.

Support for projects related to animal model development and the establishment of special animal colonies has decreased in recent years, as depicted in the following chart:

Fiscal Year	Total Active Projects	Dollars Awarded a/	Percent of Budget
1980	24	1,912	25
1981	15	1,623	23
1982	12	1,055	14
1983	7	899	11
1984	7	925	11

a/ In thousands

This reduction is in keeping with the DRR Five-Year Plan, which provided for decreased emphasis in this area, particularly of special colony projects, if funds were reduced for the program. The development and availability of important models did receive special consideration, as evidenced by the one new award in this area; i.e., the culture of the marine fanworm, Myxicola infundibulum, as a research resource. This marine polychaete has become a well-studied and useful laboratory preparation in the last few years for studies including nerve impulse generation, neuropharmacology, membrane transport, properties of axonplasm, and neurofilament structure. The feature that makes Myxicola a preparation of unusual utility is that it has a true giant axon, with a diameter comparable to squid giant axons. Problems of availability, seasonal variation in quality, etc., led to this project, which will attempt to develop and refine methods of culturing the

worm in quantities sufficient to ensure a reliable resource of quality specimens for research.

OTHER PRIMATE RESOURCES

Breeding and Development

In addition to the seven Regional Primate Research Centers, the Animal Resources Program supports several other nonhuman primate resources. These include one contract and four grants for the domestic breeding of nonhuman primates. In addition, there is a grant for a Primate Supply Information Clearinghouse. These projects are part of the effort to provide a supply of primates for essential biomedical research. The supply of rhesus monkeys from commercial and other sources is continuing to increase; therefore, the contract for production of monkeys is being allowed to terminate as scheduled on April 27, 1985. As of June 30, 1984, the inventory was 2,688 rhesus monkeys with 881 female breeders and 275 cynomolgus monkeys with 139 female breeders. There were 660 live births in the rhesus colony and 100 births in the cynomolgus colony during the past year. Sales to research institutions were 510 rhesus and 58 cynomolgus monkeys. Phase-out of the contract-supported colony has started with the sale of 270 cynomolgus and 980 rhesus monkeys to the contractor. The animals remaining in the inventory will continue to be sold or dispersed to other Public Health Service programs in a manner that encourages commercial sales.

The grant-supported primate breeding projects are designed to establish nuclear production colonies and to determine proper husbandry techniques for maintaining these colonies. Colonies under development are baboons, squirrel monkeys, and two species of Galago (bushbabies). The squirrel monkey resource is representative of this activity. Now in its fourth year of development, the colony includes 155 adult females. Reproductive performance has improved each year, with 73 pregnancies reported in 1984. Losses from stillbirths and abortions have steadily decreased, while survival of orphaned or weak infants was improved by development of an intensive care cage unit and separate nursery facility. A computer-based mathematical model was designed to predict long-range changes in the breeding colony using basic demographic statistics. This model is a promising new management tool and can be adapted easily to breeding colonies of other species. A number of studies have been carried out to characterize normal hormonal events in female and male squirrel monkeys as a first step in evaluating reproductive performance. A number of early abortions were discovered by observing changes in serum hormone concentrations. Karyotyping studies are ongoing to determine whether chromosomal anomalies are involved in these early abortions. Samples were submitted for electrophoretic analysis in order to identify biochemical genetic markers, and several polymorphic markers were identified. A series of behavioral studies have been completed to address alterations resulting from environmental varia-

bles, such as light/dark interval, cage design, and composition of the social group. This work has provided insight into new management strategies that show promise in reducing mortality and increasing breeding efficiency.

Island Colony

In addition to these breeding and development grants, the Caribbean Primate Research Center at the University of Puerto Rico has a grant supporting an island colony, which presently contains 680 rhesus monkeys in 4 intact social groups. These monkeys have genealogy records dating back to 1938, making them very useful for social, behavioral, and population demographic studies. The center also carries out a research program with primates housed at Sabana Seca on the mainland. These studies include tropical diseases, models of eye disease, and degenerative diseases in aging populations of rhesus monkeys. The National Institute of Neurological and Communicative Disorders and Stroke maintains a colony of rhesus monkeys at the center for fetal studies.

Primate Supply Information Clearinghouse

The Primate Supply Information Clearinghouse is designed to facilitate maximum research use of primates already in this country. The Clearinghouse matches requests for primates, primate tissues, and related services with investigators who, and breeding colonies that, have these items available. The Clearinghouse publishes a weekly bulletin (circulation of 1,375) and handled 1,342 formal requests for primates and 1,637 informal requests during Fiscal Year 1984. It placed 7,135 living primates and satisfied 156 requests for cadavers, tissues, and other specimens, and 26 special listings for cages, services, etc. The requests published and the primates exchanged from one facility to another have increased dramatically over the years. Requests increased by 160 percent and the number of primates increased by 170 percent in six years. A total of 27,000 animals were placed during the past six years, as determined by recontact with clients who placed advertisements. This number is probably conservative, because many persons made long-term sharing agreements after their initial advertisement through the Clearinghouse. The rate of success of placing animals via the Clearinghouse has been high, ranging from 70 to 90 percent in recent years. The Clearinghouse has also facilitated some research that might not otherwise have been possible. For example, a number of monkeys with naturally occurring strabismus were found for an investigator studying amblyopia.

INSTITUTIONAL ANIMAL RESOURCE IMPROVEMENTS

Institutional animal resource improvement projects are awarded to help institutions upgrade their animal facilities and develop centralized programs of animal care to support their biomedical research programs. A major objective is to enable institutions to comply with the Animal Welfare Act and DHHS policies on the care and treatment of animals. Requests of

this type are usually for animal cages to meet current regulations, general sanitation equipment, such as cage washers, renovation of animal facilities, and addition of trained professional and technical personnel. The projects are supported for one to three years, after which the applicant institution is expected to take over complete financial responsibility for its basic animal resource.

Institutional improvement projects have been supported since the inception of the Laboratory Animal Sciences Program. This area received increased emphasis in Fiscal Year 1972, when Congress appropriated an additional $1.5 million to help research institutions achieve compliance with the Animal Welfare Act of 1970 (Public Law 91-579). The NIH policy on "Care and Treatment of Laboratory Animals" (issued June 14, 1971) and the subsequent DHHS policy on "Animal Welfare" (issued May 14, 1973) also contributed to the overall response in this area. During the past 14 years, 125 institutions have received improvement grants, with awards totaling approximately $17.3 million. The following table shows the levels of activity in recent years.

Fiscal Year	Reviewed	Approved	New Awards	Total Active Projects	Dollars Awarded a/	Percent of Budget
1971	9	5	1	14	673	11
1972	21	15	19	24	2,169	35
1973	86	62	15	28	2,318	37
1974	19	12	36 b/	46	3,217	55
1975	21	17	19 b/	38	2,582	42
1976	19	9	6	21	1,259	22
1977	14	7	6	13	1,054	19
1978	21	13	3	11	793	12
1979	9	7	4	7	709	11
1980	12	8	4	6	783	10
1981	16	16	2	7	298	4
1982	17	16	5	7	697	10
1983	4	4	2	2	229	3
1984	6	4	4	5	489	6

a/ In thousands
b/ Includes applications reviewed in previous year

The chart indicates a relatively steady rate of new proposals until Fiscal Year 1983. Both considerable interest in this program area and substantial institutional need for assistance remain, as indicated by the National Survey of Laboratory Animal Facilities and Resources (published March 1980; Fiscal Year 1978 data). In recent years, however, emphasis has been placed on funding new projects of other types and on combating inflationary costs. Recognition that institutional animal resource improvement awards were limited resulted in a decrease in the number of new applications. In recent fiscal years, including this year, specific budget proposals have been made in the Animal Resources Program for major new funding in this area. Support for new construction has also been requested.

RESOURCE LABORATORIES

The objectives of resource laboratories are:

- o to provide improved animal health programs through appropriate surveillance and investigation of naturally occurring disease and other laboratory animal problems;
- o to support studies resulting in new information on diseases of laboratory animals and their etiology;
- o to aid in the elucidation of new animal models of human disease; and
- o to develop resources for research and training.

Resource laboratories have been a major program activity for more than ten years. Most resource laboratories are institutional in nature; however, in several instances, more than one institution in a metropolitan or regional area has been served. Institutions receiving such awards have shown a continuing turnover (support has been terminated for 14 laboratories). The total number has remained relatively constant (13-16) in recent years. Approximately 41 percent of the budget is awarded in this area.

The value of vendor surveillance is continually demonstrated by these resources. One program was able to detect the presence of Tyzzer's disease in rabbits from a commercial supplier before any animals were shipped to either the university or a Veterans Administration (VA) hospital. Diagnostic efforts are ongoing to deter introduction of this serious disease into laboratory colonies. This example and other initiatives of the resource were instrumental in initiating a barrier system at a VA hospital and in convincing the administration, as part of a new building program, to design a specific pathogen-free (SPF) facility, with a clean/dirty corridor design, and to use SPF animals in research programs.

One resource has expanded its monitoring activities beyond the usual disease-oriented approaches and has developed a genetic monitoring program

for common strains of rats and mice. Standard isoenzyme techniques are currently being used for mice. However, the resource has developed strain specific antisera for six of the most common strains of rats. Previously reported in England, this technique has not been routinely employed in this country. It does offer several advantages over current monitoring approaches for rats. A current paper based on experience with this technique will help establish its utility for other laboratories.

Screening of new arrivals and surveillance and monitoring of in-house animals are aimed at recognition and elimination of disease problems before they can interfere with research. One resource went one step further by initiating a minimal-disease rabbit colony in collaboration with a commercial rabbitry. Defined flora, SPF stock was provided to the rabbitry, which developed a highly productive breeding nucleus using new facilities and barrier methods. The resource has continued to monitor the colony and to date has found no evidence of infectious diseases. Facilities are now being expanded to increase production, and the goal is to provide minimal-disease rabbits for routine use in research. This experience provides clear evidence of commercial feasibility of raising rabbits free of those common infectious diseases which seriously compromise research using conventional rabbits.

That the larval stage of Taenia taeniaeformis, the common tapeworm of cats, induces sarcoma of the liver in chronically infected laboratory rats has been known for more than 60 years, but carcinogenic effects of other taeniid cestodes have not been reported. One resource recently observed the occurrence of a highly anaplastic sarcoma associated with long-term infections (1.5-2 years) involving larval stages of Echinococcus and a second species of Taenia. Both were being maintained in the laboratory by means of serial intraperitoneal transfer. The tumors produced by these cestodes were histologically identical and apparently were derived from mesothelial cells. That associated with the larval Echinococcus was found to be uniformly transferrable to rodents of the same species by means of inoculation of ascitic fluid or tumor fragments intraperitoneally or subcutaneously. This report demonstrates that other taeniid larvae that proliferate or persist in the peritoneal cavity of rodents may have a carcinogenic effect when maintained for long periods of time.

Collaboration with investigators to solve a problem of naturally occurring diseases was exemplified by one resource. A breeding colony of mice involved in embryo transplant research experienced increasing morbidity and decreasing fertility. It was determined that several viral pathogens were present in the colony and many mice were seropositive for Mycoplasma. Because the research dictated maintaining mice in a conventional mode without barrier protection, the only option was rederivation of mice within the colony. A joint effort was initiated to transplant embryos from contaminated donor mice to disease-free mothers, which were placed in an isolator. Following delivery, the rederived mice were placed in new,

decontaminated rooms and breeding was commenced. The rederived stock has remained free of Mycoplasma infection, and breeding performance and experimental data are once again satisfactory. This alternative rederivation procedure saved considerable time and expense compared to standard Caesarean rederivation techniques and may prove to have useful application under other circumstances.

Complications associated with Mycoplasma infection were also demonstrated by another resource. Investigators studying adjuvant and collagen-induced arthritis in Lewis rats were not able to induce arthritis consistently. After considerable diagnostic effort and a series of experimental studies, Mycoplasma pulmonis was found to be responsible for modulating the onset and course of the arthritis. Because murine mycoplasmosis is the most common infection of rats, this demonstration of alteration of the immune system, particularly cell-mediated immunity, is extremely important. Ongoing studies are examining which T cell subsets are associated with the inflammatory lesions of chronic arthritis and the influence of Mycoplasma infection on T cell subsets and the production of interleukins.

Attempts to control murine mycoplasmosis are underway at another resource. Two temperature-sensitive mutants of Mycoplasma pulmonis have been produced and tested for pathogenicity in SPF Fischer 344 rats. One mutant produced a mild rhinitis, while the other caused no significant lesions. Preliminary challenge experiments indicated that the vaccine afforded a significant degree of protection. Passive transfer of sensitized spleen cells and sera from vaccinated animals to naive animals resulted in protection from challenge for spleen cell-inoculated animals, but not those inoculated with sera. This indicates that the rat immune response to M. pulmonis is cell-mediated and not humorally mediated. Current studies are examining the antigenicity of extracted membrane fractions and the influence of M. pulmonis on natural killer cell activity. Development of an effective vaccine and a better understanding of the modulating effects of mycoplasmosis on the immune system will be extremely important in dealing with this important laboratory animal disease.

It is clear that mouse hepatitis virus (MHV) is prevalent among populations of laboratory mice. Its ubiquity is becoming especially apparent with the development and use of sensitive new serodiagnostic tests. Several resources have examined patterns of MHV infection and interactions with other infectious agents. The failure of mice to seroconvert to pneumonia virus and reduction in serum antibody to Sendai virus were shown to be associated with previous infection with MHV. These results have important implications for laboratory animal diagnostic efforts, immunologists, and investigators studying the biology of viral infections in mice.

Vaccination with killed Sendai virus vaccine has been routinely employed in animal facilities to protect highly susceptible mouse strains against Sendai virus infection. In addition to causing appreciable morbidity and mortality

in mice, Sendai virus has been shown to be immunosuppressive in rodents. To determine what effect vaccination has on the immune response, one resource studied Balb/c mice for six weeks following vaccination. Assays included the proliferative responses of spleen cells to mitogens triggering T and B lymphocytes, natural killer activity, induction of alloimmune, cytolytic T cells *in vitro*, and the induction *in vivo* of both cellular and humoral immunity to sheep erythrocytes as measured by delayed-type hypersensitivity (DTH) and direct plaque-forming cells (PFC). It was found that 50 to 80 percent of vaccinated mice had moderate to severe immune dysfunction more than three weeks after vaccination; by five to six weeks, responses in all mice were within normal limits. The data suggested that cells belonging to the subset of T lymphocytes, or alternatively, an accessory cell required for their responses, were most affected by vaccination. Hence, investigators using recently vaccinated mice should be aware of this influence on the immune response in planning their experiments.

Rotaviruses are important causes of intestinal infection among newborns and the young. Laboratory mice are susceptible to the murine rotavirus, which causes a syndrome known as epizootic diarrhea of infant mice (EDIM). One resource used a mouse model to study the course of the replication of the virus in the intestine, the relationship of viral replication to immunity and disease, and the effects of the animal's age on these parameters. Using reagents specific for the mouse virus, investigators found that diarrhea was produced in animals only when they were inoculated at one or seven days of age. Viral replication was also most extensive in the two youngest groups, but it could be detected at lower levels in animals inoculated at 14 days of age and, minimally, in those inoculated at 21 and 28 days. A pronounced rotavirus intestinal antibody response was seen by post-inoculation day seven in all inoculated mice, including older animals in which viral replication was limited. Conclusions of this study were that rotavirus enzyme immunoassays using EDIM virus antigen and EDIM virus antibody are simple, sensitive, and reproducible. Also, rotavirus-seronegative mice of all ages are susceptible to this infection; however, the extent of viral replication declines as mice age, especially after 14 days, and correlates with the extent of intestinal virus replication. Finally, it appears that EDIM is an excellent, although under used, model of rotaviral infection.

OTHER RESOURCE ACTIVITIES

The Laboratory Animal Sciences Program (LASP) provides partial support for the Institutes of Laboratory Animal Resources (ILAR) of the National Academy of Sciences and for the accreditation program of the American Association for Accreditation of Laboratory Animal Care. The former project serves the biomedical community by providing scientific and technical information on laboratory animal resources, including guidelines for animal care, use and breeding; planning and conducting of conferences and symposia; and promoting high-quality, humane care of laboratory animals. ILAR carries out its

program through a small staff and committees of recognized scientists and experts from the scientific community. A number of other Government agencies also provide general support.

Other LASP information projects include support for the Laboratory Primate Newsletter, the Registry of Avian Genetic Stocks, and publication of a handbook of marine invertebrate development. The latter project will provide investigators with ready access to information on methods for collecting adults, obtaining gametes, and maintaining a broad range of marine invertebrate species. The handbook is intended to give investigators a broad comparative introduction to the development of marine invertebrates and their use as research tools and to encourage pursuit of research on a large complex of processes and phenomena occurring in invertebrate marine animals. Approximately half of the 30 chapters originally outlined are nearing completion, and the remaining chapters are expected to be ready for publication by early 1985.

Reference Centers

The LASP currently provides partial support to three reference center projects. The first is the Registry of Comparative Pathology, located at the Armed Forces Institute of Pathology. The registry has continued to augment its collection of specimens from primates and other laboratory animals, domestic and wild animals, fish, and birds. Material has been made available to others and is used in the preparation of exhibits, lantern, and microscopic slide sets, and as the basis for a number of publications. The registry responds to numerous outside requests for consultation and publishes a quarterly Comparative Pathology Bulletin to promote communication and information dissemination to the biomedical community. The Bulletin is mailed to more than 1,100 addresses. Since 1972, it has been responsible for preparing one or two descriptions of an animal model of human disease for publication each month in the American Journal of Pathology. A handbook entitled Animal Models of Human Disease has been prepared for sale; 12 fascicles covering 281 models, with a cumulative index, have been published so far. An annual three-day course in comparative pathology was offered for the 11th time in May 1984.

The second project is the Simian Virus Diagnostic Laboratory at the Southwest Foundation for Biomedical Research, San Antonio, Texas. The primary purposes of this laboratory are:

- o to provide definitive virus diagnostic services, including identification and characterization of viruses that may be present in primate tissues;

- o to develop and maintain a working repository of simian viruses and prepare reference seed virus and specific antisera to these viruses;

- to provide consultation services and encourage the pooling of information and exchange of viral agents among primate centers and other health organizations; and

- to train interested students in virological laboratory procedures associated with primate investigations.

During the last reporting period, a total of 1,393 serum specimens, 45 specimens for virus isolation, and 16 viruses for identification were received from 49 institutions.

A relatively new reference center activity is located at the Jackson Laboratory. The long-term objective of this project, entitled "Cryopreservation of Murine Germplasm," is to establish a bank of frozen mouse embryos to preserve mutants and strains of mice that are valuable to many fields of research. In many cases, cryopreservation will allow a reduction in the number or size of colonies maintained by conventional breeding procedures and will retard genetic drift. Freezing techniques, using eight-cell embryos frozen at a controlled rate and stored in liquid nitrogen, are now well established. More than 350,000 embryos have been frozen and stored from approximately 350 different strains since the project's inception three years ago. To date, more than 40 strains have been terminated from active breeding because embryos have been safely preserved.

MANPOWER DEVELOPMENT

Training in laboratory animal medicine is intended to prepare individuals to provide professional care for the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through knowledge of laboratory animal biology and understanding of research methods. In addition, trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests, either as independent investigators or as members of a research team.

Currently, there are 9 active (T32) institutional post-doctoral training programs with a total of 32 funded trainee positions. One institutional short-term (summer) training program (six trainee positions) also is funded. Three individual post-doctoral fellowships were supported during Fiscal Year 1984. Because the average training period of the post-doctoral programs is 2 1/2 years, there are usually 10-12 graduates per year. Currently available figures indicate that 203 trainees and fellows have completed training since the inception of the training grants and fellowships in laboratory animal science and medicine; 66 of these are employed by medical schools and 77 by other academic, research, or Governmental organizations. The majority (118) are serving as directors or staff members of a vivarium; 68 are

engaged in teaching and research or are obtaining additional training; and 17 are in public health, private practice, retired, or deceased. Retention in the field of laboratory animal medicine has been excellent, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such persons.

For the past nine years, the active training programs and diagnostic resources have been encouraged to employ veterinary students during their summer break. Over the past year, 9 programs involving 17 students participated. Critiques of the students involved were submitted to the program and, in turn, distributed to all the Program Directors. A follow-up study of 146 DVM graduates who spent one or more summers at an ARP resource was carried out during the year. It was found that 34 individuals (23 percent) engaged in formal post-doctoral academic training (excluding internships and residencies), while an additional 15 persons (10 percent) were in academic or research positions. Over the past four years, nearly 45 percent of appointments to ARP post-doctoral training programs have come from this pool of summer trainees.

As the specialty field of laboratory animal medicine has matured, many of its members have found, upon completion of their training, that the demands for research resource activities have been overwhelming. Further, most recent graduates do not have the depth of research experience in a particular discipline to allow them to compete for regular research grants. To meet the need for additional experience and time for full-time research, a new research career development program, the Special Emphasis Research Career Award (SERCA) in Laboratory Animal Science, was established in 1982. This special award offers in-depth experience for the laboratory animal specialist in various fundamental and clinical scientific disciplines. It is made to develop multidisciplinary veterinary researchers who will direct their research toward refining the use of laboratory animals in biomedical research, the study of significant laboratory animal disease problems occurring in vivarial settings, and the development of new animal models useful in solving biomedical research problems. Four awardees are currently in the second year of their program. During Fiscal Year 1984, a total of four SERCA applications were received; three were recommended for approval and one was awarded. The research training of this new awardee will focus on a host-parasite system as a model of hypersensitivity reactions in the small intestine.

FUTURE DIRECTIONS

The Laboratory Animal Sciences Program plans will continue to emphasize its support for projects aimed at the etiology, pathogenesis, diagnosis, and control of significant laboratory animal diseases. Projects will focus on viral diseases in rodents because of the large numbers of rodents used in research and the demonstrated impact of many of these diseases. Animal

model and special colony projects have decreased in number in recent years. Support for primate breeding activities will continue to be shifted to the user community and private industry. The ability to fund institutional animal resource improvement projects will depend upon the appropriation of additional funds for this activity. The current number of diagnostic resources and institutional training programs will be continued. Manpower development will be emphasized through individual fellowships and the SERCA program to the extent that funds can be made available for this purpose. The full impact of the Small Business Innovation Research Program on the above activities remains to be determined. The amount set aside in Fiscal Year 1984 under the SBIR Program was based on 0.6 percent of the Animal Resources Program appropriation. This set-aside will increase in future years (Fiscal Year 1985, 1 percent; Fiscal Years 1986 and 1987, 1.25 percent).

BIOMEDICAL RESEARCH MODELS DEVELOPMENT

The Biomedical Research Models Development Program is exploring the use of cell systems, lower organisms, and nonbiological systems as models in biomedical research sponsored by the NIH. Such model systems can provide cost-effective resources to the research community where they can serve as simple, effective, or efficient representations of complex biological phenomena.

An evaluation of the relevance and limitations of such systems as models in biomedical research is in process. The National Academy of Sciences (NAS), under a contract from the NIH administered by the Division of Research Resources, is carrying out this evaluation. If the results of the NAS study (workshops) indicate that such an activity is both necessary and meritorious, an extramural grants program in Biomedical Research Model Development will be initiated.

The Division is continuing to maintain the database needed to identify and track research projects using mammalian and nonmammalian models.

DESCRIPTION

The development of models is an important need in science and a key element in DRR's mission. In addition, the development of a model is often essential to the understanding of complex biological phenomena. Some research activities can use simpler systems as models (lower organisms, tissues and cells in culture, or nonliving systems) when seeking to answer questions of universal biological processes. Simpler model systems often provide data which are expensive, difficult, or impossible to obtain using higher animals as models. From a scientific perspective, it is advisable to

determine if any of these specific simpler systems has general applicability. Intensive interest focuses on such developments today because of their potential for accelerating research findings, dealing with multiple variables, and reducing the current costs of biomedical research.

The Biomedical Research Model Development activity is intended to foster the development and evaluation of biomedically important research methodologies based on lower organisms and nonliving models. The use of such models is invaluable in many areas of NIH-supported research. For example, invertebrate model systems can be employed to study such diverse areas as basic aspects of vitamin metabolism, the control of enzyme biosynthesis, metal ion toxicology, and hepatocellular carcinoma. Projects currently underway are using insects and nematodes in basic studies of the biology, biochemistry, and genetics in aging. Cell and tissue culture-based biological assays are also used in studies of a variety of physiologic phenomena.

The wide range of biomedical research activities involving models which differ phylogenetically, structurally, and conceptually is apparent from an ongoing DRR inventory of the research methods and models employed in Public Health Service (PHS)-supported research projects. This inventory makes possible the identification of research models employing lower organisms, tissues and cells in culture, or nonliving systems; individual investigators having established expertise in these areas of potential model development; and trends in the use of such systems by the several NIH Institutes.

STATUS OF NAS EVALUATION

DRR's contract activity with the National Academy of Sciences for an evaluation of models in biomedical research is nearing completion. The steering committee, selected by the Commission on Life Sciences, held six workshops exploring the use of lower organisms, in vitro techniques, and mathematical approaches in the development of models for biomedical research.

The titles of the individual workshops were:

- Model Systems in Cellular Immunology;
- Models for the Investigation of Learning;
- Non-Mammalian Models for the Study of Biological Regulation;
- Models for the Study of Diseases and Aging;
- Study of Development Using Non-Mammalian Models; and
- Mathematical Modeling in Biomedical Research.

Summaries of each workshop, together with abstracts of the presentations, have been submitted to the steering committee that is evaluating model systems in biomedical research. A complete initial draft of the committee's report is expected in October, and the final report should be delivered to NIH on January 25, 1985.

TRENDS IN MODEL SYSTEMS IN NIH EXTRAMURAL RESEARCH

The Branch has prepared a report giving trends in use of biological systems as research models in NIH programs for the NAS steering committee evaluating "Models in Biomedical Research." The Office of Technology Assessment requested copies of this report for use in their Congressionally requested study of "Alternatives to Animal Use in Testing and Experimentation." The Office of Policy Planning and Evaluation of the Environmental Protection Agency also sought copies to serve as background material in its study of short-term bioassays and their potential importance in future regulatory policy.

FUTURE DIRECTIONS

A specific extramural program in Biomedical Research Model Development will be developed if the results of the workshops indicate that such an activity is both necessary and meritorious. Assuming that the results are favorable, the Division will prepare estimates of total funding required, and the criteria for allocating and administering funds. Requests for grant applications could be issued as early as 1985, with initial awards being made in 1986, or early in 1987.

ADMINISTRATIVE ISSUES

Revision of the NIH Guide for the Care and Use of Laboratory Animals is underway, and is expected to be available by March 1985; it will reflect the large number of comments delivered in three public hearings, and the even larger number submitted in writing. Both the animal welfare community and research scientists have submitted lengthy documents. (See the Laboratory Animal Sciences Program section.)

The report by the National Academy of Sciences on "Models in Biomedical Research" is proceeding on schedule. (See the Biomedical Research Model Development section.)

The Trans-NIH Coordinating Committee for Research Animal Resources met eight times during Fiscal Year 1984. Members reviewed NIH issues, such as the site visits made by Office of Extramural Research and Training teams to grantee institutions, the proposed Office of Protection from Research Risks (OPRR) revisions of the NIH Assurance Program, and the OPRR proposal for an education program for grantee administrative and scientific staffs using animals. At the September meeting, they heard a detailed discussion of the evolution of animal welfare laws in Switzerland and of the recent attempt to have a national referendum forbidding the use of animals in research in Swiss research programs. This referendum is supposed to come to a vote next year.

The committee also coordinated its efforts with the NIH Intramural Animal Care Committee, both of which are to be listed as regular committees in the NIH telephone directory. The Committee functioned as an information exchange for the NIH intramural and extramural laboratory animal interests. Subjects considered included:

- o references and data on animal use;
- o security of the laboratory animal facility;
- o Congressional bills and resolutions concerning animals in research;
- o Congressional and other studies of the laboratory animal field;
- o activities of animal welfare and animal rights groups; and
- o the effect of new Federal policy changes on animal facility management.

Table I

Primate Research Centers Program Applications - FY 1984

Application Types	Number Rec'd.	Amount a/ Req'd.	Number Appr.	Amount a/ Appr.	Number Funded	Amount b/ Funded
New.....	--	--	--	--	--	--
Renewal.....	2	6,666,619	2	6,640,872	2	6,364,433
Supplemental..	7	1,531,368	7	1,529,168	7	1,529,168
Continuation..	5	17,947,614	5	16,018,926	5	14,467,570
TOTALS	14	26,145,614	14	24,188,966	14	22,361,171

Table II

Laboratory Animal Sciences Program Applications - FY 1984

Application Types	Number Rec'd.	Amount a/ Req'd.	Number Appr.	Amount a/ Appr.	Number Funded	Amount b/ Funded
New.....	43	3,780,864	33	2,316,913	18	1,723,849
Renewal.....	18	2,672,367	17	1,829,635	12	1,723,206
Admin. Supp..	4	349,420	4	349,420	4	477,712
Compet. Supp.	--	--	--	--	--	--
Continuation.	32	3,814,143	32	3,076,177	31	4,243,062
TOTALS	97	10,616,794	86	7,572,145	65	8,167,829

Table III

Laboratory Animal Sciences Programs - FY 1984

Programs	Number Rec'd.	Amount a/ Req'd.	Number Appr.	Amount a/ Appr.	Number Funded	Amount b/ Funded
Resource Rsch.	28	2,325,012	24	1,766,135	14	1,378,322
Prim. Resource	5	1,103,556	5	820,801	4	756,580
Colon.& Models	14	1,589,355	11	1,060,398	7	924,739
Basic Improve.	8	1,008,650	6	481,232	5	488,931
Diagnostic Lab	17	3,430,292	17	2,447,854	16	3,403,950
Reference	3	388,282	3	318,456	3	521,079
Information	9	258,516	9	244,314	8	317,994
Research Career	8	351,716	7	309,661	5	237,252
New Investig.	5	161,415	4	123,294	3	138,982
TOTALS	97	10,616,794	86	7,572,145	65	8,167,829

a/ Direct costs
b/ Indirect costs included

Table IV

Application Activity and Application Types - FY 1984

Activity and Types	Number Rec'd.	Amount a/ Req'd.	Number Appr.	Amount a/ Appr.	Number Funded	Amount b/ Funded
P40						
Type 1...	16	1,791,264	11	895,941	8	853,637
Type 2...	15	2,417,943	14	1,595,251	10	1,519,538
Type 3...	4	349,420	4	349,420	4	477,712
Type 5...	20	3,309,203	20	2,580,384	20	3,646,420
TOTALS	55	7,867,830	49	5,420,996	42	6,497,307
R24						
Type 1...	12	1,304,473	11	971,658	7	765,328
Type 2...	2	169,604	2	149,564	2	203,668
Type 3...	--	--	--	--	--	--
Type 5...	5	253,562	5	250,864	5	303,612
TOTALS	19	1,727,639	18	1,372,086	13	1,272,608
K01						
Type 1...	4	178,017	3	136,834	1	49,788
Type 2...	--	--	--	--	--	--
Type 3...	--	--	--	--	--	--
Type 5...	4	173,699	4	172,827	4	187,464
TOTALS	8	351,716	7	309,661	5	237,252
R23						
Type 1...	3	96,700	2	58,579	1	44,429
Type 2...	--	--	--	--	--	--
Type 3...	--	--	--	--	--	--
Type 5...	2	64,715	2	64,715	2	94,553
TOTALS	5	161,415	4	123,294	3	138,982
R13						
Type 1...	1	15,000	1	15,000	--	--
Type 2...	--	--	--	--	--	--
Type 3...	--	--	--	--	--	--
Type 5...	1	12,964	1	7,387	1	11,013
TOTALS	2	27,964	2	22,387	1	11,013
R01						
Type 1...	6	376,760	4	228,876	--	--
Type 2...	1	84,820	1	84,820	--	--
Type 3...	--	--	--	--	--	--
Type 5...	--	--	--	--	--	--
TOTALS	7	461,580	5	313,696	--	--
R25						
Type 1...	1	18,650	1	10,025	1	10,667
Type 2...	--	--	--	--	--	--
Type 3...	--	--	--	--	--	--
Type 5...	--	--	--	--	--	--
TOTALS	1	18,650	1	10,025	1	10,667
GRAND TOTALS	97	10,616,794	86	7,572,145	65	8,167,829

a/ Direct costs
b/ Indirect costs included

Table V

Training Program Applications - FY 1984

Application Types	Number Rec'd.	Amount a/ Req'd.	Number Appr.	Amount a/ Appr.	Number Funded	Amount b/ Funded
New.....	9	173,991	8	140,518	1	17,388
Renewal.....	--	--	--	--	--	--
Supplemental..	--	--	--	--	--	--
Continuation..	12	1,111,776	12	1,154,436	12	690,612
TOTALS	21	1,285,767	20	1,294,954	13	708,000

Table VI

Training Programs - FY 1984

Programs	Number Rec'd.	Amount a/ Req'd.	Number Appr.	Amount a/ Appr.	Number Funded	Amount b/ Funded
NRSA-Institu.	9	1,054,842	9	1,097,502	9	635,745
NRSA-Individ.	10	193,762	9	176,722	3	61,884
Short-Term	2	37,163	2	20,730	1	10,371
TOTALS	21	1,285,767	20	1,294,954	13	708,000

Table VII

Contract Program - FY 1984

Programs	Number Rec'd.	Amount Requested	Number Approved	Amount Approved	Number Funded	Amount Funded
Primate Res.	--	--	--	--	--	--
Other Prog. Act	1	95,000	1	95,000	1	95,000
TOTALS	1	95,000	1	95,000	1	95,000

Table VIII

Small Business Innovation Research Applications - Phase I

Application Types	Number Rec'd.	Amount a/ Req'd.	Number Appr.	Amount a/ Appr.	Number Funded	Amount b/ Funded
New (RR Prim.)	1	41,037	--	--	--	--
New (RR Secd.)	2	56,641	1	38,115	--	--
New (RR Only)	5	194,503	3	90,449	2	102,368
TOTALS	8	292,181	4	128,564	2	102,368

a/ Direct costs
b/ Indirect costs included

Table IX

Small Business Innovation Research Applications - Phase II

Application Types	Number Rec'd.	Amount a/ Req'd.	Number Appr.	Amount a/ Appr.	Number Funded	Amount b/ Funded
New (RR Prim.)	1	161,473	--	--	--	--
New (RR Secd.)	1	181,452	--	--	--	--
New (RR Only)	--	--	--	--	--	--
TOTALS	2	342,925	--	--	--	--

Table X

Summary of Tables

Tables	Number Rec'd.	Amount a/ Req'd.	Number Appr.	Amount a/ Appr.	Number Funded	Amount b/ Funded
I.....	14	26,145,601	14	24,188,966	14	22,361,171
II, III and IV	97	10,616,794	86	7,572,145	65	8,167,829
V and VI.....	21	1,285,767	20	1,294,954	13	708,000
VII.....	1	95,000	1	95,000	1	95,000
VIII.....	8	292,181	4	128,564	2	102,368
IX.....	2	342,925	--	--	--	--
TOTALS	143	38,778,268	125	33,279,629	95	31,434,368

a/ Direct costs
b/ Indirect costs included

Biomedical Research Support Program

INTRODUCTION

The Biomedical Research Support (BRS) Program consists of three distinct activities: the Biomedical Research Support Grant (BRSG) Program, the BRS Shared Instrumentation Grant (SIG) Program, and the Minority High School Student Research Apprentice Program (RAP). The authorizing legislation allows NIH to fund research grants for general support to strengthen institutional research in sciences related to health.

BIOMEDICAL RESEARCH SUPPORT GRANTS (BRSG)

The objective of the BRSG activity is to strengthen and enhance the research environment of institutions heavily engaged in health-related research through the use of flexible funds and local decision-making, which enable them to conduct their biomedical research programs more efficiently and effectively.

The Program extends opportunity and responsibility for scientific administrative leadership to the institutional level, where specific on-site allocations can be made for biomedical research purposes. Through local decision-making, this procedure allows for a balance of internal institutional needs and early recognition and development of emerging research concepts, techniques, and talent.

Biomedical Research Support Grants are designed to complement other types of Public Health Service research programs and are made annually to institutions that are heavily engaged in health research. BRSG funds provide flexible support which enables institutions to respond quickly and effectively to the emerging opportunities and unexpected requirements that develop frequently in the course of research.

Appropriate uses, developed through a combination of institutional self-determinations, NIH program intent, and Congressional oversight, include:

- o pilot research;
- o support of new investigators;
- o unexpected research requirements and emergencies;

- o continuation of research during temporary interruption of grant support;
- o emerging research opportunities;
- o establishment of new laboratories;
- o improvement of investigators' research skills;
- o investigations in new fields and in fields new to the investigator;
- o central shared research resources;
- o compliance with animal welfare requirements; and
- o research opportunities for minorities and women.

Awards are made to nonprofit institutions, not directly to individual investigators. Health professional schools, other academic institutions, hospitals, state and municipal health agencies, and research organizations may apply if the institution received a minimum of three allowable PHS biomedical or health-related behavioral research grants, totaling $200,000 (including direct and indirect costs). Federal institutions and institutions located in a foreign country are not eligible. The amount of each BRSG award is based on a formula that is applied to the total of direct and indirect costs awarded for allowable PHS research grants, as shown in Table I.

Table I
Calculation of BRSG Awards, FY 1984 a/

	Computation Percentage	Research Grants Base Increments		
I.	15%	$ 0	to	$ 900,000
II.	10%	$ 900,001	to	$ 3,600,000
III.	6%	$ 3,600,001	to	$10,800,000
IV.	.6%	$10,800,001	and	above

a/ Total of increments I through IV x 0.28077918 (proration factor) = award amount

INVESTIGATOR-INITIATED PROJECTS

BRSG typically supports research projects for which investigators submit applications for BRSG funds directly to their institution's BRSG advisory committee. Such BRSG investigator-initiated projects include pilot projects, regular projects, and inaterim support. Whether or not the BRSG committee funds these projects depends on such factors as scientific merit, the criteria cited by the committee, and the institution's priorities for the use of discretionary funds. For example, the committee may prefer projects dealing with a particular science, or new investigators, or prefer to fund as many viable projects as possible, given limited resources. Types of investigator initiated projects in terms of their objectives are presented below.

Pilot Projects

As their name implies, investigators pursue new scientific ideas and directions in pilot research projects. Normally a pilot project produces experimental evidence of the potential efficacy of a new approach. The results usually will be disseminated to other investigators, regardless of the project's outcome: A positive outcome makes investigators aware of a promising new direction in research; a negative outcome provides general information and preempts unnecessary replication of unproductive efforts. The project is expected to yield the information and justification for an application to sponsor further research, if warranted.

Regular Projects

In a regular project, the expectations are quite different, but the outcomes are not less beneficial to the overall maintenance and development of research. The purpose of BRSG support of a regular project is to meet an unexpected requirement or to pursue an emerging opportunity associated with an existing sponsored research project. Regular projects are undertaken by investigators who are already conducting sponsored research.

Interim Support

In contrast, interim support is provided to investigators who are not currently conducting sponsored research. The established investigator who needs funds to maintain an animal colony in the unfunded period between sponsored projects typifies the recipient of interim support.

CENTRAL RESOURCES

Central resources such as equipment and research facilities are expensive to maintain, particularly in comparison to the funds needed for many pilot or

other projects. Consequently, it is important to institutions that BRSG funds, or a portion of them, may be carried forward from one year to the next. This provision permits institutions to allocate funds (e.g., $25,000) for the purchase of expensive equipment without interrupting the funding of pilot projects and other efforts requiring comparatively small allocations (e.g., $3,500 per project). Of course, grantees may also choose to expend the entire BRSG award in one year on a single purchase if such an investment if given priority.

BRSG funding of central resources usually requires a joint effort among several investigators, departments, or other beneficiaries in the institution. For example, a BRSG committee or Program Director may decide to fund major purchases because several investigators have jointly requested a specific central resource, because there is a general effort to enhance the capability of a particular department or science, or because the Dean or Program Director has continually received requests for a specific central resource. The institution may also use BRSG funds to maintain the costs of lab equipment at animal facilities (e.g., services to users) or to upgrade facilities (e.g., renovations for animal labs).

OTHER INSTITUTIONAL ACTIVITIES

BRSG funds serve other uses within the institutions. Although such activities often involve the support of research or equipment, their primary intent is more far-reaching in terms of meeting broad institutional objectives.

Recruitment

Recruitment activities are an important strategy for building institutional capabilities in targeted areas. Recruitment priorities are defined by administrative personnel, the BRSG committee, the BRSG Program Director, or by another governing research committee. For all cases, some type of negotiation of resources occurs before employment. BRSG funds are then used to provide the recruited investigator with the resources needed for his or her research as soon as possible, after arrival at the institution.

Collaborative Projects

Opportunities for collaborative efforts are also frequently stated as an objective for BRSG projects, although collaboration may be seen as a secondary benefit to another primary research objective. The availability of seed money through BRSG permits initial testing of fresh ideas and provides the resources necessary to explore new areas, and thus provides an incentive for scientists and clinicians with different areas of expertise to discuss a collaborative proposal. Collaboration can also be cost-effective

as investigators pool their resources, for example, laboratory equipment and human subjects in the clinical setting for research. It also provides a means for professional growth by giving basic researchers the chance to develop applications of their work and enabling clinicians to become more involved in research.

SPECIFIC BRSG ACTIVITIES

Sustains Valuable Research Resources

An eastern university used BRSG funds to continue to maintain its on-site World Health Organization (WHO) Collaborating Center for Reference and Research on Pneumococci. Additional support is pending from other sources, including the National Institute on Aging, to maintain the laboratory in the future.

For the past 15 years, a major undertaking of its Department of Research Medicine has been to conduct studies leading to the redevelopment and licensure of a polyvalent vaccine of pneumococcal capsular polysaccharides for the prophylaxis of pneumococcal infection. The vaccine has been designed to prevent infection in those segments of the population recognized to be at risk of serious or fatal illness if invaded by these organisms. As a result of these efforts, a vaccine containing 14 capsular antigens was licensed in the United States in 1977 and, subsequently, in a number of other nations. Because of this department's role in these developments, the World Health Organization designated it as one of the two WHO Collaborating Centers for Reference and Research on Pneumococci. The other center is located in the Danish State Serum Institute in Copenhagen. Other than the Centers for Disease Control (CDC) in Atlanta, Georgia, these two laboratories are the only laboratories in the world that possess the reagents necessary to carry out definitive studies of the epidemiology of pneumococcal types causing illness in man, and budgetary reductions have recently caused sharp cutbacks in CDC activities in this area.

Helps Launch New Department

In 1979, a new Department of Radiation Oncology was established at an eastern medical center. During the department's infancy, BRS funds provided support to help launch its research program and strengthen its ability to attract outside funds. In 1980, a new faculty member received $4,000 in BRS funds for a study on immune effects on radiocurability of mouse tumors, and a second member received $4,948 for a study of biological effects of ionizing radiation at the molecular, cellular, and organismal levels. In 1981, a third person received $24,500 for studies in radiation therapy. BRS funds also enabled the department to purchase a shared resource used by

investigators who are working on projects requiring ionizing radiation. The department now attracts about $250,000 a year in outside research support, and recently it received a three-year grant totaling approximately $230,000 from a private foundation for studies to predict tumor and normal tissue response to clinical radiotherapy. It also received research support from the Department of Energy for continuing studies on the biological effects of ionizing radiation, is participating in an NIH-supported radiation therapy oncology group, and has grants from the American Cancer Society. Thus, a modest contribution of BRS funds has led to major funding for the department and has promoted research in the area of cancer treatment and effects of radiation.

Fosters Collaborative Research

Earlier findings, derived from a southern medical school laboratory, suggested that hormones can greatly influence memory storage of new information. A project was designed to test the possibility that the hormones might affect brain mechanisms that are responsible for storing the new information. This project therefore examined the possibility that, like true memory, hormones could regulate the formation of long-term potentiation. The findings indicate that peripheral injections of epinephrine, or some adrenergic agonists, can enhance the development of long-term potentiation. The dose-response characteristics are remarkably similar to those seen in behavioral studies of drug effect on memory.

These findings have several important implications. First, they suggest that hormonal influences on behaviorally assessed memory may result from regulation of the neuronal systems that can change and thereby store new information. Second, they indicate that, although epinephrine is injected systemically and does not itself enter the brain, it can have large effects on brain function. Third, they provide a new procedure with which to evaluate the cell biological mechanisms that underlie long-term potentiation and, perhaps, memory. These studies required development of new technology which could combine the different methodologies of behavioral research on memory and of neurophysiology. Because the experiments spanned two research areas, one of which involved procedures the laboratory had not previously used, it is very unlikely that independent Federal funding could have been obtained. Thus, the BRS support enabled the development of a project that integrated two previously unrelated subareas and established a line of research in this laboratory which will continue for the next several years.

Stimulates Research in New Area

A 1978-79 Biomedical Research Support Grant Annual Progress Report from a New York research organization described a project titled "Establishment of Human Epidermal Cell Strains and Study of Their Differentiation In Vitro." The availability of BRSG funds enabled this study to provide a method and basic data for growth of epidermal cells *in vitro* in the absence of feeder

layers. Such a system was in great demand for use in dermatology, cell biology, transplantation, immunology, and virology. Investigations of the potential use of tissue-cultured skin for treatment of burn patients were initiated. In 1981, the National Science Foundation awarded a grant to study the "Growth and Differentiation of Epidermal Langerhans Cells and Melanocytes, and Their Interactions with Keratinocytes," work stemming in part from the BRSG project. In the NSF study, the growth, differentiation, and interactions of these three cell types, their dependence on known factors such as cyclic AMP inducers and/or hydrocortisone, and the effect of products of one cell type on another were investigated. Based on this work, new research has been proposed to the U.S. Army Medical Research and Development Command on "Wound Coverage by Cultured Skin Cells." This research, which is expected to be funded during 1984, proposes to accomplish the following:

- o refine the established systems for producing epidermal sheets from cultures of human keratinocytes in order to enhance their use as grafts in humans;

- o expand clinical experience with autografts of epidermal sheets;

- o determine where grafting sheets of allogeneic epidermis can be used to promote wound healing; and

- o explore the mechanisms responsible for graft rejection or graft acceptance with epidermal cells grown in tissue culture and/or modified in vitro.

These investigations should improve the present technology for using tissue-cultured cells in treating wounds. They also will provide data that will permit the evaluation of possibilities for using allogeneic, epidermal cell-tissue transplant between individuals of a single species in wound healing.

Resource Critical to Investigation of Unexpected Deaths

In the mid-1970s a southern medical school used BRSG funds to purchase a transmission electron microscope. This equipment was intended to serve as the main piece of instrumentation in a research histopathology laboratory. The laboratory itself was designated as a central resource to aid all investigators who needed histologic and ultrastructural studies to support their research ventures. At least one R01 grant application has been funded, in part as a result of the histologic and ultrastructural pilot studies. The number of additional individual grants approved and funded because of continuing support from this central facility can not be determined accurately. It is clear, however, that the current director of the histopathology resource laboratory has interacted with every research investigator at this center, as well as with many others in nearby institutions. Recently the value of the histopathology resource laboratory has received additional recognition as the result of a study being conducted

in rats fed unusual diets. The histopathology laboratory found that the animals developed fatty livers, a condition thought to be attributable to their diets. The main study was part of an RO1-supported research project. These observations became more significant when a neonatologist investigating the unexpected deaths of a number of low birth weight infants received reports that the infants had fatty livers. When the physician sought published material, the librarian informed him of the rat research study. Conversations followed between the neonatologist and the research scientist, and led at least in part to the preliminary conclusion that a new vitamin E supplement may be involved. The FDA was informed, use of the vitamin was suspended, and Congressional hearings were held. It is the feeling that prompt recognition of the possible problem was facilitated by knowledge of the basic research project, and by the existence of the histopathology laboratory, funded by BRS.

Develops Animal Model

An example of research supported by BRSG funds which also has direct significance for human disease is a project initiated by the Department of Otorhinolaryngology of a midwestern medical school. The pilot project, entitled "Inner Ear Changes in the Ferret Model for Reye's Syndrome," was performed in collaboration with other investigators within the same department and within the Department of Pediatrics and Communicable Diseases. The researcher and his colleagues were able to develop and use the ferret as an animal model for study of Reye's syndrome (RS).

Reye's syndrome is a potentially fatal illness which occurs in children following a brief viral illness, usually influenza or chickenpox. The role of influenza infection or its interaction with other etiologic agents (e.g., aspirin) is difficult to study in patients because infection occurs well before RS is diagnosed. Thus, an animal model such as the ferret is extremely useful in studying the etiologic factors and their interactions in this disease. The ferret is appropriate for such studies because it is extremely susceptible to human influenza infections. As a result of BRSG support for this pilot project, the investigators have three publications in press or recently submitted detailing their findings. One abstract has also resulted from this work, as well as two papers presented at national meetings. The pilot project also provided the basis for a recently funded NIH proposal entitled "Microscopic Studies of the Inner Ear."

Generates Additional Support

A significant outcome of the appropriate use of BRSG funds for the support of pilot studies can be measured in terms of the funds which later are made available by Federal and non-Federal agencies for the research initiated through the BRSG mechanism. Faculty investigators from a southwestern medical school have successfully obtained this support as documented by an analysis made of BRSG-supported investigators and awards received. Between

April 1, 1980 and January 1984, funds were allocated for 115 pilot projects reviewed by the internal BRSG committee. From July 1, 1981 through May 28, 1984--the period commencing a year after the first of the reported BRSG allocations--32 members of the faculty who received BRSG pilot support were awarded external grants totaling $3,092,414. This support came from 13 different private agencies and 2 Federal departments.

EVALUATION OF THE BRSG PROGRAM

As first noted in DRR's Fiscal Year 1981 Annual Report, the fourth evaluation of the Program was initiated because of the General Accounting Office's concern that "...the BRSG objectives, as currently established, appear too general to permit NIH to effectively measure the extent to which they are met."

Subsequently, a Request for Proposals (RFP) was issued to conduct a short-term (six-month; approximately $100,000) evaluation of the Biomedical Research Support Grant Program. The RFP called for the contractor:

- to review and revise the BRSG Program Performance Summary prepared by the Program staff;
- to develop measures of the progress and success of the Program in achieving its objectives;
- to assemble, analyze, and summarize data on program performance in terms of the Program's objective as proposed in the first two items;
- to specify processes for data collection, reporting, and analysis that will optimize the Program staff's ability to monitor progress and success; and
- to characterize long-term, full-scale evaluations of the Program that could be taken.

Aurora Associates, Inc., of Washington, D.C., was selected as the contractor and the evaluation process was begun in February 1983. The evaluation consisted of four phases: (1) an evaluability assessment of the BRSG Program; (2) a plan for data collection and analysis; (3) a synthesis of nine on-site case studies of BRSG grantee institutions; and (4) alternatives for evaluating and monitoring the BRSG Program.

The evaluation study concluded that:

- o Program format is consistent with and supports the attainment of Program objectives.
- o The BRSG Program's emphasis on decentralized decision-making allows institutions to target resources to areas that contribute to institutional research and development strategies.
- o BRSG funds are highly coveted by investigators and administrators because of their flexibility and the institution's ability to administer them on a quick-turnaround basis.
- o The BRSG Program generally is administered with a high degree of rigor and formality in the institutions, possibly because the funds are valued and seriously competed for by investigators and programs within the institutions.
- o BRSG Program funds are reaching the programs, departments, and investigators for which they are intended, and as far as this study can judge, are resulting in impressive benefits.
- o No evidence was found to suggest that a more restrictive definition of BRSG fund usage would increase Program performance; if anything, the results suggest that increased restrictiveness could be counter-productive.
- o Little, if any, program or cost benefit would be derived from increasing or greatly modifying requirements for monitoring grantee institutions.

This study reaffirms the value and benefits of the Biomedical Research Support Grant to both the grantee institutions and the research programs of the National Institutes of Health.

MINORITY HIGH SCHOOL STUDENT RESEARCH APPRENTICE GRANTS

The purpose of the apprentice program is to stimulate in minority high school students a broader interest in careers in science. Eligible institutions are those that were awarded grants during the latest complete Federal fiscal year from either the Biomedical Research Support Grant (BRSG) Program or the Minority Biomedical Research Support (MBRS) Program. Only one application for the Apprentice Program can be submitted by the recipient of both the BRSG and MBRS awards. Support is provided at a level of $1,500 for each apprentice position allocated. These funds are provided as a separate award, and are accounted for and reported separately. No indirect costs are paid. Direct support to the apprentice must be as salary. Funds

not required for apprentice salaries may be used to enrich the research experience, add additional apprentices, or extend the period of research participation. The funds can be used only for costs of the apprentice program and for no other purpose. Each institution to which apprentice support is awarded will be responsible for designation of a Program Director. The Program Director is responsible for recruitment and selection of the apprentices and assignment of each to an investigator. Each apprentice should be offered a minimum of eight weeks of full-time experience. Salaries should be at the prevailing scale for comparable work and in no case less than the Federal minimum wage. Selection of students for the Program should take into account factors such as ability and scholastic accomplishment. No socio-economic constraints are placed on the eligibility of the students. Assignments should be made to investigators involved in health-related research who are committed to developing in the high school students both an understanding of the research in which they participate and the technical skills involved.

The Office of the Director, NIH, assigned responsibility for conducting the NIH effort to the Biomedical Research Support Program (BRSP) in the Division of Research Resources. An apprenticeship program began with $400,000 and 200 student positions in Fiscal Year 1980. The first year, 100 institutions, those receiving the largest BRSG awards, were eligible; 45 institutions applied and received support for students.

In 1981, NIH broadened eligibility to include all BRSP grantee institutions (approximately 500) as well as those receiving Minority Biomedical Research Support (MBRS) awards from DRR (approximately 75). The budget was increased to $1 million which permitted support for 666 student positions. The budget has remained at this level in subsequent years.

In 1981, 38 percent of the eligible institutions applied and received an average of 2.9 student positions (range, 1 to 4). By 1984, 45 percent of the eligible institutions applied and received an average of 2.3 student positions (range, 1 to 3). Since the inception of the Program in 1980, some 405 different institutions have participated for at least one of the five years; approximately 72 percent of these institutions have been active three to four years. A concern has been expressed that with an increasing number of eligible BRSG and MBRS institutions requesting student positions (an average of 11 per year), under the current allocation process, there will be concomitant decrease in the number for each institution. Thus, the issue of a "critical mass" of students has arisen.

As part of the its overall evaluation activities, and to expand its knowledge base of the Program's operations at the institutional level, the Division initiated a series of discussions with its National Advisory Research Resources Council and the Biomedical Research Support Subcommittee of the its General Research Support Review Committee on the future directions of the Minority High School Student Research Apprentice Program.

To assist in this process, a meeting was held at the NIH on April 24, 1984, with a group of 23 Research Apprentice Program Directors and grantee institution officials who had expressed a special interest in the Program through recent conversation or correspondence. A summary of that meeting follows:

- o General: The Program Directors, mentors, and students strongly support continuation and expansion of the Program.

- o Recruitment and Selection of Students: The diversity of factors involved calls for guidelines that continue to allow flexibility to deal with the variety of needs.

- o Enrichment Curriculum: Each institution must tailor its curriculum to the special needs of its students and mentors, as well as the resources available to, and other responsibilities of, the Program Directors.

- o Peer Interaction/Critical Mass: Criticality of numbers of students was highly dependent upon the resources and environment of the institution involved. However, the need for more student positions was evident, and increased fiscal resources are needed.

- o Award Considerations: The present self-election allocation option appeared to be the most appropriate, and increased fiscal resources could diminish some of its limitations.

- o Evaluation Considerations: There was a recognition that evaluation was a necessary part of the overall program, but it should be practical and not burdensome.

RECOMMENDATIONS

The following set of operating recommendations were then developed by the Program staff and accepted by the National Advisory Research Resources Council:

- o The objective of the Reseach Apprentice Program should (1) continue to reflect the 1979 intent of the White House Office of Science and Technology Policy; (2) be general in nature; and (3) allow a diversity of approaches. Therefore, the following language has been adopted: "To stimulate a broader interest in minority high school students in careers in science."

- o The recruitment and selection of students should continue to emphasize factors of the students' motivation, ability, and scholastic aptitude and accomplishments. In addition, consideration should be given to science teachers' recommendations and, where possible, the degree of

parental commitment. Socio-economic factors should be of secondary consideration.

- The precise number of student positions that should be made available to each of the various types of eligible applicant institutions was difficult to determine. However, it was recognized that a "critical mass" of students is necessary for the development and execution of a successful curriculum. This desirable level could be reached, in the majority of cases, with four to six students.

FUTURE DIRECTIONS

On September 1, 1984, the Program was reannounced for Fiscal Year 1985, and eligible institutions were informed that applications were due by December 1, 1984. They were also informed that (1) limited funds and increased requests for such student positions may restrict the final allocations by DRR to three or four students; and that (2) upon recommendation of the National Advisory Research Resources Council, the Division will give preference in making awards to institutions that can support a summer program having a "critical mass" of at least five to six students using institutional as well as DRR funds.

BRS SHARED INSTRUMENTATION GRANT (SIG) PROGRAM

Through this Program, DRR provides for the acquisition of sophisticated, state-of-the-art instrumentation which is becoming an increasingly important tool for biomedical research and which is essential to maintain this country's position in the forefront of technology. The overall SIG Program objective is to make available to institutions major research instrumentation on a shared-use basis for groups of NIH-funded investigators.

The form for such research support is a competitive grant. A major core user group of three or more NIH grantees from any organization that receives a Biomedical Research Support Grant may request institutional proposals for instrumentation. Applications are considered for instruments that cost at least $100,000. There is no upper limit on the cost of the instrument funded, but the maximum award is $300,000. Special study sections of the Division of Research Grants review applications for scientific and technical merit; the National Advisory Research Resources Council conducts the programmatic review.

Fiscal Year 1984 marked the third year of operation for the SIG Program. From its beginning in 1982, the Program has grown steadily. Because of budget increases, it was able to increase the number of awards for large-

scale instrumentation shared among individuals, research groups, departments, and institutions from 23 in 1982 to 115 in 1984 (see Table II). A similiar strengthening of programs has also occurred in the Department of Defense and the National Science Foundation in order to address the problem of replacement and renewal of research-shared instrumentation.

ASSESSMENT OF THE SIG PROGRAM

To determine the types of instruments requested and the magnitude of need for the large-scale shared instruments, a three-year assessment of the program has been made and data have been gathered across a broad sample of institutions.

An analysis of the application data by type of institution indicates that medical schools and graduate schools (in approximately the same ratio) account for an increasing number of instrument requests from 68 percent in 1982 to 81 percent in 1984. Research organizations rank a distant third, followed by hospitals and other health professional schools. Each year, the number of grants awarded has been directly proportional to the number of applications submitted by each type of institution.

From the sample of all applying institutions, the applicants' needs for new instrumentation in the $100,000 to $300,000 range were assessed. The six instrument types requested most frequently were: electron microscopes, cell sorters, nuclear magnetic resonance (NMR) spectrometers, mass spectrometers, macromolecular sequencers, and image analysis/computer graphics systems. These six instrument types constituted 82 percent of the needs of the applicant institutions over the three-year period. Electron microscope instruments dominated the requested list in all years.

Instruments less commonly requested included x-ray diffractometers, fermentation systems, laser-based instruments, raman, infrared, and fluorescence spectrometers. Other requests, mainly by clinical investigators, included a variety of radiological equipment ranging from ultrasound to positron emission tomographs. Many of the requests are for new commercial instruments that have incorporated microcomputer systems which greatly increase the data acquisition, reduction, and display of capabilities. Introduction of new NMR technologies has also led to a number of new requests for *in vivo* NMR instrumentation.

A summary of the award data by type of instrument is shown in Figure I. These charts demonstrate that the peer review system has led to a fairly equitable distribution of instrumentation awards. The percentage of awards for each type of instrument is roughly proportional to the number of applications submitted for each type of instrument.

Perhaps the most direct indication of the trans-NIH nature of the SIG Program is the distribution of NIH research grants of the investigators requesting the instrumentation. Since the Program's inception in Fiscal Year 1982, the distribution of NIH-funded research grants of the major users has remained fairly stable. The National Cancer (NCI); General Medical Sciences (NIGMS); Heart, Lung and Blood (NHLBI); Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK); and Allergy and Infectious Diseases (NIAID) Institutes are the major supporters of the investigators. Although all NIH Institutes provide funds to investigators, this is nearly the same rank order in which these Institutes award NIH research project grants.

Figure II presents the aggregate data for Fiscal Year 1982-84. Approximately the same percentages of research grants per Institute are represented in the SIG awards as in the applications submitted, with no clustering of awards to any one Institute. The slightly higher award rate to NIGMS is accounted for by the fact that in Fiscal Year 1984, the SIG Program funded 12 dual-assignment applications from that Institute.

The first SIG instrumentation facility was dedicated January 25, 1984. The occasion commemorated the installation of a new research laboratory for computer-based image processing at Washington University's School of Medicine in St. Louis, Missouri. This technology is playing an increasingly important role in research. The interactive system consists of a flatbed scanner, image processor, camera, and computer systems. The instrumentation will speed up the storage, manipulation, and projection of data, and is currently being used by a large number of NIH-funded researchers to analyze autoradiograms, slides, gels, and photographs of patients.

FUTURE DIRECTIONS

Access to the unique capabilities provided by modern, up-to-date instrumentation has benefited a broad group of basic and clinical investigators.

For the future, the SIG Program will concentrate on strengthening the research capabilities of NIH-funded investigators by providing large-scale major instrumentation on a shared-use basis. As shown in Table II, in three years of operation, the availability of SIG Program dollars has occasioned a very substantial response from the biomedical community. More than $100 million has been requested; 229 awards totaling $37.4 million have been provided to 1,881 NIH-funded researchers.

Obviously, instrumentation in the $100,000 to $300,000 range is not only an acute problem today, but will continue to be a problem in the future, because technological progress quickly renders instrumentation obsolete. With the growing use of microprocessors, the development of new technologies, and the demand to update equipment, institutions will always face

pressures to improve instrumentation, especially that shared by a broad group of users. A continuing program is needed to provide NIH researchers with instrumentation sophisticated enough to deal with today's complex challenges in biomedical research.

Table II

Shared Instrumentation Grant Funding History

Fiscal Year	Number of Applications	Total $ Requested (in millions)	Number of Awards	Total $ Awarded (in millions)
1982	205	$39.1	23	$ 3.7
1983	160	$30.4	91	$14.0
1984	166	$36.2	115	$19.7

Biomedical Research Support
Shared Instrumentation Grant Program
Application and Award Distribution, FY 1982-84
by Type of Instrument

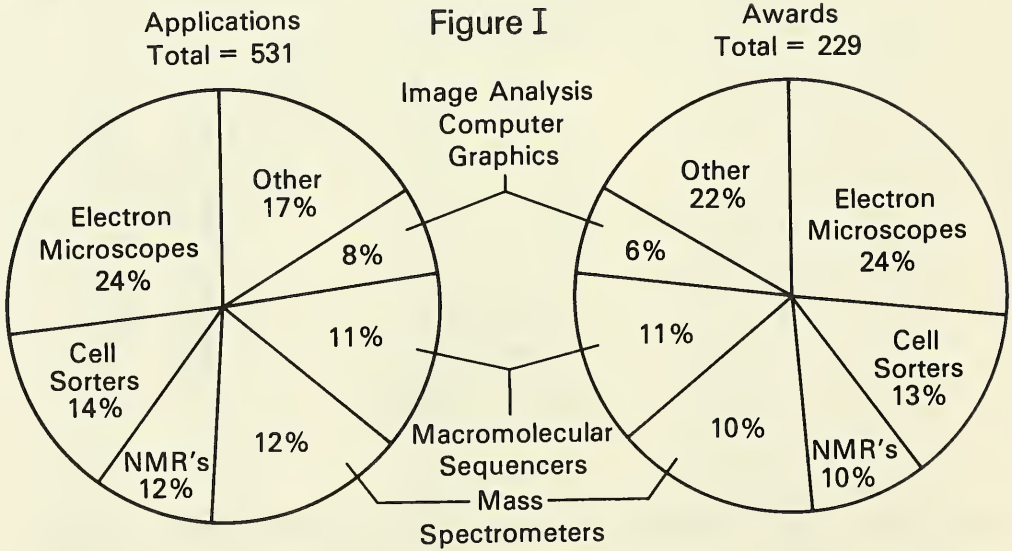
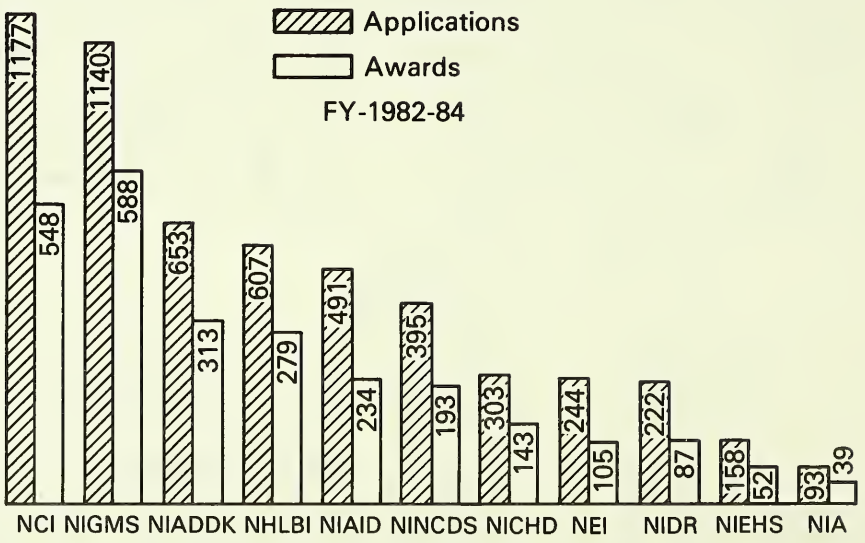


Figure II

NIH Research Grants to Major SIG Users



Biomedical Research Technology Program

INTRODUCTION

The Biomedical Research Technology (BRT) Program was initiated in 1962 after Congress expressed interest in the establishment by NIH of an activity focused on specialized technology needed for biomedical research. Since that time, the BRT Program (formerly called Special Research Resources and Biotechnology Resources) has modified and expanded its scope. In the early years, the Program mainly supported large general-purpose computer centers in medical schools. It later moved into an extremely broad and innovative array of biomedical technologies. The Program now places greater emphasis on regional and national sharing of resources. Today, it focuses on applications of knowledge engineering, information technology, biomedical engineering and digital technology for biomedical and clinical research programs, and technologies for the study of biomolecular and cellular structure and function.

PROGRAM TRENDS

During Fiscal Year 1984, the BRT Program funded a variety of new awards. These included 4 resource grants, 1 resource cooperative agreement, 4 resource-related research project grants, 12 supplements to resource grants to enhance training activities, 22 small grants, and 7 small business innovation research grants. Some of these awards are briefly described below.

NUCLEAR MAGNETIC RESONANCE (NMR)

A grant was awarded to Dr. John Leigh of the University of Pennsylvania, Philadelphia, to support a resource in *in vivo* NMR. In addition to core research projects on probe and coil design, an extensive series of experiments relating energy and substrate metabolism to disease state or other conditions is planned.

A resource on NMR imaging and *in vivo* spectroscopy was established at the University of Florida in Gainesville under Dr. Katherine Scott. The resource will emphasize collaborative projects on human and animal metabolism, and will provide advice and support for the diagnostic imaging studies conducted on the existing imaging system.

A resource development grant was awarded to Dr. Irwin Kuntz at the University of California, San Francisco, to explore the broad usefulness of two-dimensional Fourier transform NMR in deriving and elucidating peptide and protein structure in solution. This is an area of great interest in NMR, and Drs. Kuntz and G. M. Crippen developed a novel algorithm to use spectral data to derive spatial and geometrical information on structure.

SEQUENCE ANALYSIS

A resource cooperative agreement was awarded to IntelliGenetics, Inc., in Palo Alto, California, to provide on-line network access to nucleic acid sequence databases, primarily GenBank (TM), and analysis programs. The proposal is to develop an interacting community with shared interests to plan experiments and develop software through network involvement with other scientists. Dr. Eugene Kromer is the Principal Investigator, and Dr. Dennis Smith is the Resource Manager and user contact. Users were accepted in the autumn of 1984, and full activities should be implemented within six months. A cooperative agreement is similar to a grant, but the Government retains more authority, in this case to ensure the separation of commercial and public interests.

A Protein Identification Resource (PIR) was established at the National Biomedical Research Foundation, Georgetown University, Washington, D.C., to provide database searching and sequence analyses techniques to aid in protein identification. The PIR incorporates the National Biomedical Research Foundation Protein Sequence Database and several nucleic acid sequence databases. The resource will also develop computer systems to predict medical significance of proteins based on amino acid sequences and facilitate associative browsing in sequences and to stimulate insight from this browsing.

MOLECULAR MECHANICS

A grant was awarded to Dr. Norman L. Allinger at the University of Georgia, Athens, to continue his work in the development of molecular mechanics, an empirically based computational technique for the prediction of molecular structures and energies. Molecular mechanics allows relatively simple and accurate calculation of the properties of a wide range of molecules. Dr. Allinger will extend the program to more complex biomolecules. His new work will be available to scientists through the PROPHET System and the Quantum Chemistry Program Exchange.

SYNCHROTRON X-RAY MICROPROBE ANALYSIS

A new resource at Brookhaven National Laboratory, Upton, New York, will offer the life science community the opportunity to exploit an emerging new

technique of X-ray microprobe analysis. The source of intense, tunable X-rays at the National Synchrotron Light Source will make it possible for the first time to do multi-element specific analyses of trace materials to levels of ten parts per million spatially localized to a few micrometers and analyses of single elements to levels of three parts per billion in a 5-micron spot. The analysis is performed in a nondestructive way in relatively favorable environments for biological materials.

HIGH-VOLTAGE ELECTRON MICROSCOPY (HVEM)

A resource-related research project grant was awarded to Dr. Joachim Frank of New York State Department of Health, Albany, to develop methods to permit three-dimensional computer reconstruction of projection images obtained in the high-voltage electron microscope. Micrographs of thick sections from a tilt series will be digitized and three-dimensional reconstruction will be performed with a computer using a modified back projection algorithm. Another grant in HVEM was awarded to Dr. Conly L. Reider, also of the New York State Department of Health, to develop HVEM techniques for the study of mechanisms of mitosis and meiosis.

TRAINING SUPPLEMENTS

In February the Program announced a planned expansion of training in resources. The training is intended to enable biomedical scientists to become more effective users of resource technologies. As a result of this announcement, the Program made 11 supplemental awards for training. (See discussion below.)

MASS SPECTROMETRY

Awards made to the University of California, San Francisco, and to Washington University, St. Louis, Missouri, will enable visiting scientists to obtain "hands-on" instruction in mass spectrometry. Funds are available for travel and subsistence for short-term (one to four months) training. An award made to the University of Colorado, Denver, resource will support a four-day course on applications of mass spectrometry to clinical research.

SPECTROSCOPY, DIFFRACTION, AND CELLULAR FUNCTION RESOURCES

An award to the University of Pennsylvania, Philadelphia, provides funds for a formal training in data analyses, methodology, and special techniques needed to study structures of proteins with X-ray absorption spectroscopy using synchrotron radiation. Funds are available for travel and subsistence

for training at synchrotron facilities at the University of Pennsylvania; Stanford University, Palo Alto; Cornell University, Ithaca; and Brookhaven National Laboratory.

Funds were provided to the Resource for Crystallography at the University of California, San Diego, to produce a videotape to train protein crystallographers in the use of the multiwire area detector diffractometer. This videotape will be used to familiarize scientists with the diffractometer system before they come to the resource.

The National Biomedical Electron Spin Resonance Center, Milwaukee, Wisconsin, received an award to provide one-on-one training in electron spin resonance. Travel and subsistence money is available for two-week visits to the resource.

An expanded training program at the National Center for Biomedical Infrared Spectroscopy, Columbus, Ohio, was funded. Travel and subsistence will be provided to visiting graduate students for short- or intermediate-term (approximately four months) and long-term (one year) training in Fourier transform infrared spectroscopy.

The National Vibrating Probe Resource, Woods Hole, Massachusetts, will expand its personal training and hands-on experience in the use of the vibrating probe to study small currents in living tissues. Travel and subsistence money is available for two to four months of training at the Marine Biological Laboratory at Woods Hole, Massachusetts.

BIOMEDICAL COMPUTING

An award to expand the training program at the Protein Identification Resource at Georgetown University will provide funds for travel and subsistence for visiting scientists to work with resource senior scientists for a period of two months. Visiting scientists will receive in-depth training in the use of the system and in applying its capabilities to a research problem.

The Microprocessor Resource at Rockefeller University, New York City, will conduct a two-week summer laboratory and lecture workshop in how to interface laboratory instrumentation with personal computers. The workshop will give scientists in-depth knowledge in the use of low-cost personal computers with research laboratory equipment.

SMALL BUSINESS INNOVATION RESEARCH (SBIR) GRANTS

The seven SBIR grants funded ranged in size from $22,070 for a Phase I award to $93,292 for the Phase II award. The total amount awarded was approximately $290,000.

The activities funded include:

- o further development of silicon avalanche photodiodes for positron emission tomographic imaging (Phase II);
- o tongue-activated controller which enables high-level paraplegics and quadraplegics to have computer input and device control;
- o inexpensive approach to optical character recognition for use in reading data from clinical records; and
- o development of multiple detectors using coulometric electrodes for liquid chromatography systems.

SMALL GRANTS

The total amount awarded for the 22 small grants was approximately $450,000. These grants cover a wide range of new types of technologies. Included are grants:

- o to explore the feasibilities of electron spin resonance (ESR) imaging and *in vivo* ESR spectroscopy;
- o investigate use of an alternative monocrystalline gem (sapphire) to diamond as a cutting edge in ultramicrometry for electron microscopy;
- o examine the influence of a radiofrequency field on protein partitioning during high-pressure liquid chromatography; and
- o to test the feasibility of using a thermo-acoustic sensing technique to measure temperature in and heat removal capacity of small volumes of tissue noninvasively.

RESEARCH HIGHLIGHTS

MASS SPECTROMETRY

Large proteins are difficult to sequence using conventional techniques. It is now common practice to determine the amino acid sequence of such proteins by translating the base sequence of the corresponding gene. Base sequencing methods are quite reliable, but insertions, deletions, and amide assignments do cause problems. Dr. Klaus Biemann's resource at the Massachusetts

Institute of Technology, Cambridge, has developed methods to confirm and extend protein sequence data by using fast atom bombardment (FAB) ionization techniques to examine tryptic or chymotryptic digests of small amounts of protein. Single-base errors are easily pinpointed with FAB data, and amide residues can be assigned when necessary. Dr. Biemann's resource is involved in several collaborative projects using these techniques.

ELECTRON SPECTROSCOPY FOR CHEMICAL ANALYSIS (ESCA)

A new treatment for altering the nature of the surface of the blood-contacting lining of synthetic vascular grafts has been developed in collaboration with the Electron Spectroscopy and Surface Analysis Resource at the University of Washington. This treatment, an ultrathin coating, Teflon-like in nature, is applied by the Radio Frequency (RF) plasma technique, a method widely used in the microprocessor industry. The coating is so thin that few techniques other than ESCA can even detect its presence. ESCA allows measurement of the coating to determine if it is appropriately thin and of the correct chemistry. The coating will greatly increase the ability of such vascular grafts to resist occlusion caused by blood clotting. Such occlusion frequently results in the failure of small-diameter vascular grafts in humans, and the amputation of limbs. In addition, because presently used vascular grafts occlude so readily, they cannot be used as coronary blood vessels in bypass procedures. This improved small diameter vascular prosthesis developed using RF-plasma technology may allow the saving of many limbs, and may even find utility as a coronary artery substitute. Dr. Buddy D. Ratner and his collaborators are continuing to explore the utility of this approach.

SYNCHROTRON RADIATION

X-ray data from several protein crystals have been collected at the Cornell High Energy Synchrotron Source and the macromolecular diffraction resource, directed by Dr. Keith Moffat. In particular, Dr. Michael Rossmann and his colleages from Purdue University, West Lafayette, Indiana, collected native and derivative data to high resolution on human rhinovirus crystals. The crystals are cubic, with a=445.16 A.U. Adjacent diffraction maxima were resolved by closing down the entrance slits, thus reducing beam intensity, but exposure times were still about 15 minutes per 0.3^{o} oscillation photo. Rhinoviruses are responsible for the common cold. The molecular structure of the viruses as determined from the X-ray data will aid in the study of the function of these viruses.

NUCLEAR MAGNETIC RESONANCE (NMR)

Dr. George Levy and his colleagues at the Syracuse University NMR resource in New York City have developed and are distributing general NMR data analysis software packages which are compatible with a number of computers. NMR spectra of biological materials, especially for nuclei other than protons, are often characterized by poor line shapes, rough base lines, and limited signal strength. NMR1 is a program optimized for handling such spectra, and includes decision-making capabilities which minimize opportunity for user bias. NMR1 processes one-dimensional spectra, and is in current use at more than 30 sites worldwide. NMR2 is to be distributed to test sites soon, and is a program for the analysis of two-dimensional Fourier transform NMR data. Implementation on computers with a 32-bit architecture will allow processing of very large matrices, with up to 32 million floating point data elements.

CELL SORTING

Scientists at the National Flow Cytometry Resource, Los Alamos, New Mexico, under the direction of Dr. Scott Cram are engaged in a long-range project to quantify and sort the various cell populations found in tumors. Only in the tumor itself can the host response to the tumor and the effects of treatment be evaluated. Dr. Cram's group has developed procedures to analyze and sort viable host defense cells that infiltrate a mammary carcinoma tumor (EMT6). Cells are analyzed using six parameters, including fluorescence measurements to determine DNA content, antibody labeling, and viability. Analysis software for multiparameter sorts is complex. In addition to exploring the biological problem of tumor cell populations, Dr. Cram's group is expanding the data acquisition system which is widely used for analysis of flow cytometry data.

MOLECULAR MECHANICS COMPUTING MACHINE

A special-purpose digital computing system has been designed at the Biological Computer Facility for Image Processing and Displays at Columbia University, New York City, and is now being built in collaboration with the Brookhaven National Laboratory. This system will permit the resource to provide computational power equivalent to several times that of a CRAY-1S supercomputer for energy minimization dynamics of protein molecules and interactions of proteins with other small or large molecules. The system, called FASTRUN, and its associated array processor, called MMCM (Molecular Mechanics Computing Machine), will be part of the Columbia resource, and all of the resource programs and software will be available to users. User services to the system will be provided via network connections.

MULTIPLE VISUALIZATIONS OF MOLECULES

The staff at the GRIP Interactive Graphics System for Molecular Studies at the University of North Carolina, Chapel Hill, and its scientific collaborators have developed and imported programs for producing many different geometric and parametric visualizations of molecular structure. Their work has focused on applying all available techniques to the enzyme superoxide dismutase. Various graphics techniques for producing maximum insight into the structure and function of the enzyme have been evaluated. These studies are described in a 17-minute videotape entitled "What Does a Protein Look Like?", which embodies some 40 visualizations of the superoxide dismutase molecule, and a companion paper by the resource director Dr. F. P. Brooks entitled "Views of Unseen Worlds."

EXPERT CONSULTATION SYSTEMS

A major technical impediment to routine use of computer expert consultation systems in medicine is the large amount of work required to enter patient case descriptions in the computer. Carefully designed "menu" questionnaires are useful for relatively small problems but are tedious for large medical domains. Using natural (English) language to describe patient cases is the preferred method to enter data in the computer; however, developing a system that understands natural language for reasoning in medical domains is a very difficult research problem in artificial intelligence.

Scientists at Rutgers University Research Resource on Computers in Biomedicine selected a subset of the natural language physicians use to describe patient cases. They developed a modular, front-end processing system that accepts English descriptions of patient cases and then translates them to forms that are interpreted by the general artificial intelligence consultation schemes CASNET or EXPERT. The Rutgers scientists found that this front-end processing system interpreted 85 percent of the sentences physicians use to describe glaucoma cases. Similar results were obtained for descriptions of thyroid cases. Generally, natural language front-end systems that are targeted at disease areas can be constructed for use with general consultation systems. These results indicate that an interactive modular front-end system that understands a major part of case description given in natural language can be developed. The remaining part would be obtained by questions asked of the physician by the computer. Such a system would represent a considerable improvement over current schemes for data entry to expert systems.

COMPUTER SYSTEM WITH MULTIPLE PROCESSORS

Over the past years, the Rockefeller University Microprocessor Biotechnology Resource has designed and fabricated a variety of multiprocessor systems based on single-chip computers for use in studying human and animal homeostasis, promoting rehabilitation, and serving as a basis for prosthetic

devices. These systems permit rapid processing of data from multiple inputs and use of the reduced data for control and reinforcement. Recently this resource developed a simplified and higher-speed analogue of the IEEE 488 Instrumentation Bus which standardizes and modularizes these multiprocessor systems. The new hardware with appropriate software support will be used in a number of collaborative research projects. The system will permit modularity and interchangeability of parts and programs in the various projects. This new system will be especially useful in a study of alcohol addiction in a colony of mice. In this study, 50 channels of food intake and activity data are divided into groups. Each group has its own preprocessor and memory to concentrate data, which are then transferred over a high-speed instrumentation bus to a common host computer. In this particular study, the system concentrates data of intensity and rate such that an inexpensive personal computer can summarize the data from diverse sensors, store the processed data, and effect control actions.

NEW IMAGE RECONSTRUCTION TECHNIQUES

The Computer Resource at the Mayo Foundation has developed a new computer program for conventional X-ray CT scanners which greatly improves the images of the heart obtained from a CT scan. The new technique incorporates scanning geometry and timing of X-ray CT machines and produces images in successive time intervals. The technique gives high resolution images with fewer artifacts than those obtained from data taken at a given point in time. The scheme is readily adaptable to current X-ray CT systems and should provide improved images of moving organs without an increase in X-ray dose. This is particularly true for the heart, where motion causes blurring and streaks in the conventional CT scans. The new algorithm will produce sharp images for short-time intervals, during the heart beat for example, allowing dynamic organ structure and function to be measured accurately.

WORKSHOPS AND CONFERENCES

PROPHET COLLOQUIUM

The Twelfth Annual PROPHET Users' Colloquium was held May 29 to June 1, 1984, in Wakefield, Massachusetts. Approximately 100 scientists from academia, the Government, and the commercial sector attended. Scientific presentations included talks on computer simulations of aqueous biomolecular hydration analyzed in color; cataract research using the PROPHET system; designing mutagenetic modifications of alpha-globulin using PROPHET molecular graphics; and pharmacokinetic/pharmacodynamic studies with cortico-steroids. Special Interest Group meetings included sessions on Modeling, Molecules, and Personal Computers. Fourteen workshops were held in parallel sessions of seven topics each, so that attendees were able to

participate in four sessions of their choice. Topics included personal computers and PROPHET; topics in sequencing, kinetics, and risk assessment; software engineering; the PROPHET interface to MM2; NEWFITSITES: a PROPHET procedure for analyzing ligand binding data; and topics in statistics.

INTERNATIONAL EXAFS CONFERENCE

The BRT Program cosponsored the Third International EXAFS (Extended X-ray Absorption Fine Structure) Conference at Stanford University. The conference was held in July and included a large international contingent. In addition to papers on applications of EXAFS to all types of materials, several sessions dealt with theory, instrumentation, and new areas such as EXAFS in energy loss spectroscopy. Proceedings are to be published.

INTERNATIONAL SYMPOSIUM ON MASS SPECTROMETRY

An international Symposium on Mass Spectrometry in the Health and Life Sciences was held in San Francisco in September with partial support from the BRT Program. Topics presented included soft ionization techniques, use of mass spectrometry in studying metabolism of endogenous and exogenous substances, applications in clinical research and in molecular aspects of cell biology and structure analysis. Proceedings are to be published.

MASS SPECTROMETRY TASK FORCE

As part of the ongoing activities of the Biomedical Research Technology Review Committee, a task force met on September 7, 1984, to review the status of high-mass spectrometry. Dr. Catherine Fenselau and Dr. James McCloskey co-chaired the panel which included specialists in instrument areas and biochemists. The agenda included technical presentations on current capabilities, emphasizing developments over the past two years in the high-mass area, and potential applications for these new capabilities. A report from the task force will be presented to the Biomedical Research Technology Review Committee for consideration and possible recommendations for future BRT Program activities in mass spectrometry.

INTERNATIONAL SYMPOSIUM ON NEW SPECTROSCOPIC METHODS FOR BIOMEDICAL RESEARCH

The Fourth International Symposium on New Spectroscopic Methods for Biomedical Research was held in Columbus, Ohio, September 24-26, 1984, and supported in part with BRT Program funds. Applications of infrared spectroscopy and X-ray photoelectron spectroscopy to biological and biomaterials areas were discussed. Short courses in Fourier transform infrared spectroscopy and in electron spectroscopy for chemical analysis were held after the meeting.

WORKSHOP ON FUTURE DIRECTIONS IN ELECTRON MICROSCOPY

A workshop to explore future directions in transmission electron microscopy was held August 9-11 in Bloomfield Hills, Michigan, and supported in part by the BRT Program. Topics considered included new instrumentation, theoretical concepts in electron microscopy, and new scientific applications of electron microscopy. Two summary publications will appear in the EMSA Bulletin and Ultramicroscopy Journal.

PRINCIPAL INVESTIGATORS MEETING

Principal and resource investigators of biomedical research technology resources met in Washington, D.C., November 14-15, 1983. Seven resource investigators described the technologies and research currently funded by the BRT Program. Participants broke into panels and discussed relationship of resources to institutions, to DRR, NIH, and to the user community; collaborative linkages among resources; relationship of resources to industry; the BRT Program's role within NIH; future areas of opportunity. All panels discussed mechanisms for expanding training in resources. Panel leaders presented reports of the discussion panels in a plenary session held on the morning of November 15.

FUTURE DIRECTIONS

In Fiscal Year 1984, the NIH Guide for Grants and Contracts published announcements of the Program's interest in in vivo NMR and intermediate-voltage (300-500kv) electron microscopy resources. The Program funded two in vivo NMR resources in Fiscal Year 1984 and plans to fund several more in Fiscal Year 1985, as well as to establish two or more intermediate electron microscopy resources.

Plans for the future of the PROPHET Computer Resource were developed during the year. A PROPHET Advisory Panel was assembled to provide the Program advice on the future directions for PROPHET. As a result of the Panel's recommendations, a Request for Proposal for redevelopment of PROPHET's software and hardware was issued. The new generation of PROPHET, called PROPHET II, will be a distributed system capable of working on workstations and implemented on a UNIX operating system in C language. The software redesign, testing, and documentation are to be accomplished within three years beginning April 1, 1985.

A PROPHET User Committee, called OPUS (Organization of PROPHET User Scientists), was formed this past year. The Committee will identify the needs of the PROPHET community, establish its priorities, and communicate

them to the DRR. In addition, the committee will assist in the organization and planning of the annual PROPHET Colloquium. A newsletter called the OPUSLETTER was established to inform the PROPHET community of OPUS activities and decisions. The first issue was published in July and was distributed via the PROPHET system. The BRT Program staff will meet with OPUS several times a year to plan for future additions to PROPHET.

The Program is exploring the potential of new technical developments in mass spectrometry for analyzing compounds with molecular weight up to 10,000 daltons and above. These techniques allow characterization and analysis of peptides with potent regulatory endocrine or neurological activity, complex carbohydrates with roles in cell recognition, transformation and development, and rapid characterization of synthetic nucleotides. The Program will issue an announcement of its interest in this area.

Discussions have been held with National Science Foundation (NSF) about its programs in supercomputers. Applications of supercomputers for life sciences will be examined at an NSF workshop in December 1984. Based on the results of this workshop, the BRT Program will develop plans for an initiative in this area.

INTRODUCTION

MISSION

The General Clinical Research Centers (GCRC) Program has been in operation since 1959. For 15 of those years, the Program was under the direction of Dr. William R. DeCesare until his untimely death November 22, 1983. While the Division is conducting a search for a new director, the Deputy Director, DRR, is serving as the Acting Director.

The Program provides resources for 75 General Clinical Research Centers where highly qualified investigators have the opportunity to advance the knowledge of medicine in a clinical setting. Between the time of the initial center grant award in 1960 and Fiscal Year 1984, the Program has maintained support for a dynamic cadre of clinical investigators. Specific goals of centers funded by the Program are:

- to learn more about normal and abnormal body function and about the cause, progression, prevention, control, and cure of human diseases;
- to provide an optimal setting for controlled investigation by clinical scientists supported by the NIH and other organizations;
- to encourage increased collaboration among investigators in the basic and clinical sciences;
- to encourage, develop, and maintain a national corps of expert clinical investigators; and
- to provide resources that allow advances in basic scientific knowledge to be translated into methods for improved patient care.

GENERAL DESCRIPTION OF PROGRAM AND EVOLUTIONARY TRENDS

Conducting a successful clinical research protocol is highly dependent on the research setting. Thus, the centers are designed to provide the best possible environment, including the personnel and technical tools, in which researchers can provide superior care for research patients while acquiring new health knowledge.

The research capacity of the 75 centers in the GCRC Program is equivalent to that of a single 600-bed hospital devoted entirely to human studies. The centers accommodate both inpatients and outpatients, providing the specialized care needed for studies on both adults and children. Currently, 88 beds are on pediatric wards or in children's hospitals. Of the 75 centers, 66 admit pediatric patients on a regular basis. One center is devoted to research on maternal and fetal problems surrounding delivery; another is dedicated to research involving premature infants. One center is involved entirely in outpatient research, and one to dental problems.

During the 24 years of the Program's operation, use of the research beds has become more efficient; fewer beds are supported, inpatient stay is shorter, and more scientific publications are produced. A considerable share of the research is now conducted on outpatients. The cost of operating the centers, which is Program-supported, is reduced by third-party reimbursements for the necessary hospitalization costs of one-third of the patients. Over the past eight years the Program has introduced the Clinical Associate Physician (CAP) Program to support newly independent clinical investigators; over 100 persons have served in CAP positions. The well-accepted and highly successful CLINFO System for computerized handling of clinical research data is now supported for 46 centers. Core laboratories continue to be an integral part of the resources supported, and some have newly acquired sophisticated equipment such as mass spectrometers. Finally, efforts have increased in recent years to develop formal evaluations of the Program's contributions to specific advances in medicine.

Typical Center

A "typical" clinical research center can accommodate both inpatients and outpatients, and supports 1 or 2 medical program directors, 12 nurses, 3 dietitians, 2 laboratory technicians, and administrative personnel.

The average center size is about 8 beds (range, 4 to 30). Centers often contain treatment rooms, a core laboratory, a diet kitchen, patients' lounge space, a nurses' station, a conference room, and outpatient space. The GCRC Program pays the hospital costs of all patients admitted to the centers solely for research purposes. About 35 percent of patients participating in research projects require hospitalization for diagnosis or treatment; these patients are billed for this portion of their stay, usually through third-party insurers.

When patients require routine tests at a clinical research center, the hospital's clinical laboratory often handles them. But because standard hospital laboratories cannot always provide routine tests and assays with the speed or accuracy clinical investigators need, these are sometimes provided by the core laboratory. The kinds of tests core laboratories perform vary from center to center, depending on the requirements for core services. Often they are sophisticated, state-of-the-art tests needed for

clinical research by a number of center investigators but not yet available through the hospital laboratories.

The metabolic kitchen is a center component essential for maintaining its controlled environment. It provides a level of dietary control not available elsewhere in the hospital.

Among the most important elements of a center are its highly trained paramedical personnel. Nurses, dietitians, laboratory workers, and other support personnel, trained in the methodology of clinical research, perform duties essential to maintaining high clinical research standards.

CLINFO

With 15 new CLINFO awards in Fiscal Year 1984, 37 CLINFO sites serving 46 centers were operational. The response to the availability of CLINFO to clinical investigators has been very favorable. All CLINFO systems are used extensively. The VAX 11/750 hardware was awarded to all new CLINFO users, and the hardware at three sites was upgraded from the PDP 11/60 to the VAX 11/750.

A detailed analysis completed from the annual reports of 19 centers shows a total of 429 protocols by GCRC investigators and 355 by other institutional investigators using CLINFO in the past year, totalling 74,848 connect hours. CLINFO has been used in the preparation of 610 publications and 362 abstracts during the past year. The present annual cost to the GCRC Program for the 37 awarded CLINFO Systems is $6,033,627.

An electronic mailnet among CLINFO sites, recommended by the CLINFO II Advisory Committee, has been initiated between Duke University and the University of Cincinnati, using public-domain software. It will be extended to more CLINFO sites to assess its usefulness to GCRC investigators.

The fourth meeting of the Organization of System Managers (OSM) was held at the Brigham and Women's Hospital in Boston, Massachusetts November 2-4, 1983. Topics discussed were the development of CLINFO-PLUS by the purveyor of CLINFO; communication networks among CLINFO sites; CLINFO interaction with other systems, i.e., other statistical packages or parts of PROPHET; a potential for a new CLINFO system operating on microcomputers; the role of the system manager; and the possible implementation of special features such as an outpatient management module and dietary and administrative packages.

CLINICAL ASSOCIATE PHYSICIAN PROGRAM

Clinical research activities supported by the categorical institutes of the NIH and other organizations depend on a corps of well-trained clinical investigators. A serious decline in the number of young physicians entering biomedical research careers during the mid-1970s and a decrease in the support of subspecialty fellowship training prompted the GCRC Program to initiate the Clinical Associate Physician (CAP) Program. The Program, which provides post-fellowship salary support, is designed to support young medical scientists at the beginning of their careers in clinical investigation. Of the 109 persons who have completed the Program, approximately 85 percent have remained in academic medicine. To date, approximately half of those still in academic medicine have obtained NIH support for their research.

MEDICAL STUDENTS

A GCRC Program policy allows Program Directors to use up to $3,000 of awarded funds to pay stipends to medical students who conduct research on the centers. The purpose of this policy is to expose young persons to clinical research at an early stage in their careers, in the hope of fostering a long-term interest in this area. This year, 27 students at 16 centers took advantage of this opportunity.

NEW APPLICATIONS

There is currently an increased interest in applications for new General Clinical Research Centers. This is perhaps a result of the recent program emphasis on broadening the geographic availability of these resources by supporting small-scale centers. Currently, four applications are under review and four or five more are anticipated in the coming year.

AWARDS AND HONORS

Dr. Edward G. Biglieri, Program Director of the GCRC at the San Francisco General Hospital Medical Center, was recently appointed a NATO Visiting Scientist in Medicine.

Dr. Thomas Gross, Clinical Associate Physician, Perinatal Clinical Research Center at the Cleveland Metropolitan General Hospital, was awarded first

prize for research at the 1984 clinical meeting of the American College of Obstetricians and Gynecologists.

Dr. Arthur J. Atkinson, Jr., Program Director of the GCRC at Northwestern University, has been appointed Chairman for 1984-85 of the National Institute of General Medical Sciences Pharmacological Sciences Review Committee.

Dr. John Nicoloff, GCRC Program Director at the University of Southern California, delivered the Paul Starr Lecture at the September 1984 meeting of the American Thyroid Association.

Dr. John S. Adams, Clinical Associate Physician, GCRC at the University of Southern California, has received the University's Innovation Award as well as the Young Investigator Award of the American Society for Bone and Mineral Research.

Dr. R. Paul Robertson, Program Director of the GCRC at the University of Colorado, received the Creasy Visiting Professorship in May 1984.

Dr. Maria I. New, Program Director of the GCRC at Cornell University Medical College, has been named President-elect of the Lawson Wilkins Pediatric Endocrine Society.

Dr. Bruce L. Zuraw, Clinical Associate Physician, GCRC at Scripps Clinic and Research Foundation, has received the annual first place award of a fellowship from the Asthma and Allergy Foundation of America.

Dr. James H. Lui, Clinical Associate Physician, GCRC at the University of California at San Diego, was a corecipient of the 1983 Serono In-training Award of the Pacific Coast Fertility Society.

Dr. John D. Johnson, Associate Program Director of the GCRC at the University of New Mexico, was chosen President-elect of the Western Society for Pediatric Research for 1984-1985.

RESEARCH HIGHLIGHTS

The following are biomedical highlights of research that has been carried out in the centers.

Methodology

DENTAL DISORDERS

Microsensors have been developed which can monitor chemical changes at multiple intra-oral sites and transmit the data to external recording

sources. These sensors can provide information on biochemical changes in dental plaques, periodontal pockets, and saliva which can be important for studies of dental caries and gum diseases.

THROMBOCYTOPENIA

Studies using indium-111 have provided new insight into the causes of thrombocytopenia (low blood platelets), and the reasons for success or failure of certain forms of therapy. They have demonstrated that much of the thrombocytopenia in idiopathic thrombocytopenic purpura is due to deficient production of platelets as well as excessive destruction of them. Indium-111 has also been of value in identifying accessory spleens in patients who require splenectomy as a palliative procedure for their thrombocytopenia.

TRACE GAS ANALYSES

Over the last several years, the GCRCs have been involved in the clinical testing of a series of technical developments useful in the measurement of trace gases in the expired air of premature infants. These include a hydrogen analyzer which is 50-100 times as sensitive as those now in clinical use, a method for the measurement of hydrogen excretion rate in a noninvasive manner by collecting it in a head hood, and a technique for the use of end-tidal hydrogen as an estimate of hydrogen excretion rate. The hydrogen excretion test can be important in the care of infants because it can serve as an indicator of carbohydrate malabsorption and bacterial overgrowth in the intestinal tract.

ATHEROSCLEROSIS

Omega 3 fatty acids, scarce in most American diets, can be used instead of carbon-14 cholesterol as tracers for cholesterol ester incorporation and turnover in atherosclerotic plaques. This method could eliminate the necessity for administration of radioactive substances in studies of techniques for inducing regression of atherosclerosis.

INSULIN

Work on a GCRC laboratory has led to a patent for preparation methods of a highly homogeneous radioactively labeled insulin. This insulin is more suitable for biologic studies in various target tissues than is any previously available material.

NUCLEAR MAGNETIC RESONANCE (NMR)

The new technology of in vivo NMR spectroscopy of phosphorous is being applied to the diagnosis and evaluation of treatment in children with inherited metabolic defects which affect the processing of fuels and the production of energy-rich molecules. For example, a specific defect in the production of high energy phosphates was found in a patient with muscle weakness, a specific therapy designed, and the clinical and biochemical response to therapy documented.

Physiology and Pathogenesis

FOOD ALLERGY

Systematic studies have supported the long-controversial idea that food hypersensitivity is important in the pathogenesis of atopic (allergic) dermatitis, clarified the role of standard diagnostic skin tests in the evaluation of food hypersensitivity, and provided evidence that restricted diets will significantly improve the symptoms.

MACROPROLACTINEMIA

A new syndrome of elevated serum prolactin levels with normal menses can result from the secretion of a molecular form of this hormone which is seven times normal size and of low potency. The identification of this nonprogressive condition is important because it is an exception to the rule that an elevated serum prolactin level in a nonpregnant woman almost always indicates a tumor.

DEGENERATIVE KIDNEY DISEASE

Although kidney disease can cause hypertension, degenerative kidney disease can also develop as a result of longstanding essential hypertension (high blood pressure of unknown cause). It has now been learned that hypertension may disappear for five years or more if such patients receive kidney transplants, especially if the diseased kidneys are removed at the time of transplantation. This observation not only has important therapeutic implications, but it also seems to be an indication that the kidney is somehow involved in the production of essential hypertension.

SMOKING

Cigarette smoking increases the levels of plasma triglycerides and very low-density lipoproteins, while decreasing the levels of high-density lipoproteins. These lipid changes link smoking with the increased risk of

coronary artery disease observed in smokers, because they have been identified previously as major risk factors for heart disease.

Nicotine metabolism is faster in people who consume more nicotine, probably because heavy smoking induces nicotine-metabolizing enzymes in the liver. Because many people seem to smoke to maintain certain levels of nicotine in the body, the accelerated metabolism may cause heavy smokers to need to smoke still more. The metabolic tolerance to nicotine which they develop may be a determinant of addictive smoking behavior.

PSEUDOHYPOPARATHYROIDISM

Some patients with pseudohypoparathyroidism, a failure to respond to normal amounts of the parathyroid hormone, fail to respond to a number of other peptide hormones as well. An explanation has been found for this previously mysterious association of abnormal responses: It results from a defect in a cell receptor system common to several hormones.

COFFEE DRINKING

Decaffeinated coffee contains a hemodynamically active substance which affects the circulation in many of the same ways that caffeine does, raising the blood pressure and slowing the heart rate. Its effects on the electrical conduction system of the heart differ from those of caffeine, however.

DIABETES

Four segmental grafts of pancreas have been performed from nondiabetic donors to long-term diabetic identical-twin recipients. The immediate response in each case included disappearance of insulin dependence, but in those three of the four recipients who did not receive immunosuppressive therapy, glucose intolerance returned four to eight weeks later. These startling events, occurring 15-26 years after onset of the original diabetes, suggest an anamnestic re-enactment of the course of type I diabetes in the pancreas grafts, with important implications for theories of diabetes development.

Non-insulin-dependent or type II diabetes mellitus is probably a heterogeneous disorder that can result from several different pathogenetic mechanisms. One such mechanism has now been discovered: It is the synthesis and secretion of an altered insulin which has subnormal biologic activity because of a change in one of the amino acids in the protein chain which forms the molecule.

Diabetic autonomic neuropathy is a late debilitating nervous system complication of diabetes which often includes postural hypotension, an abnormal decrease in blood pressure on sudden standing which produces dizziness and malaise. This hypotension has now been traced to a failure of the autonomic neurons to produce and secrete the neurotransmitter norepinephrine in response to postural changes.

OSTEOPETROSIS

The devastating syndrome of osteopetrosis (dense bones), renal tubular acidosis, and areas of brain calcification has been found to be caused by a deficient activity of the enzyme carbonic anhydrase 2. The discovery of this new inborn error of metabolism provides important clues to the function of this enzyme in human physiology.

ACTH UNRESPONSIVENESS

The syndrome of ACTH unresponsiveness, a rare but treatable form of hypoglycemia in childhood, has been shown to result from a specific defect in ACTH receptors in the zona fasciculata, the thick middle layer of the cortex of the adrenal gland. ACTH receptors in other parts of the gland are normal.

HYPERCALCEMIA OF MALIGNANCY

Many patients with one of several different types of cancer develop elevated blood levels of calcium. About 80 percent of them have a circulating factor which mediates this hypercalcemia. Purified 30,000-fold from human tumors, it appears to be a small basic protein distinct from parathyroid hormone.

RHEUMATOID ARTHRITIS

Earlier work on a GCRC showed that most patients who develop rheumatoid arthritis have responded abnormally to an infection with the ubiquitous agent called Epstein-Barr virus. Now it has been found that in these patients, a subset of white blood cells called T lymphocytes is much less active in suppressing the proliferation of virus-infected lymphocytes than are T cells from nonrheumatoid patients. The rheumatics' T cells apparently make less of the virus infection-fighting agent interferon; this interferon deficiency has been traced in turn to a deficient production of interleukin-2, a substance necessary for the differentiation of T cells. This work suggests a rationale for a clinical trial of interferon or interleukin-2 in early rheumatoid arthritis.

Hematuria (blood in the urine) is known to be common in patients with juvenile rheumatoid arthritis. This hematuria has been found to be closely associated with elevated levels of calcium in the blood, and sometimes with renal stones. Therapeutic agents which augment calcium excretion, such as steroids, should be used with caution in children with rheumatoid arthritis.

ATAXIA

Patients with chronic G_{M2}-gangliosidosis, an inherited metabolic neurologic disease, demonstrate a failure of muscular coordination, defective speech, tremor, and paralysis of voluntary upward gaze. The gangliosidosis has been found to result from a deficiency of the enzyme beta-hexosaminidase A. This is the first identification of a biochemical abnormality associated with an inherited ataxia.

PARKINSONISM

The "on-off" phenomenon, a rapid fluctuation of clinical response in Parkinsonism patients treated with L-DOPA, may result simply from large variations in absorption of the drug caused by meals. Continuous infusion of the drug by vein produces a stable clinical state and eliminates the on-off phenomenon.

NEW HORMONES

Two new peptides resembling growth hormone-releasing hormone have been discovered in human seminal plasma. They may have a role in fertility. Also, a new oxytocin-like material has been found in amniotic fluid, urine, and cord blood, and in estrogen-stimulated human plasma. The role of this material in pregnancy is being investigated.

RENAL HYPERCALCIURIA

Renal hypercalciuria in children, unlike that in adult patients, is not associated with a diminished ability to concentrate the urine, an inability to acidify the urine, or a decreased ability to reabsorb beta-2 microglobulin in the proximal renal tubule. These findings suggest that the renal tubular dysfunction previously noted in adult patients with hypercalciuria is the result of a lifelong exposure of the nephron to a high urinary calcium concentration.

INBORN ERRORS OF UREA SYNTHESIS

Children with inherited deficiencies of enzymes of the urea cycle usually develop symptoms of hyperammonemic coma (ammonia intoxication) in the first week of life and expire at an early age. Several years ago, a therapy involving protein restriction and a stimulation of alternative pathways for waste nitrogen excretion was developed through GCRC research; this resulted in an increase in the one-year survival rate to 92 percent, a sixfold improvement over that with the best previous therapy. Studies of the survivors indicate that most of them are mentally handicapped; an important point, however, is that the impairment of intellectual function is closely linked to the duration of the coma. This finding makes aggressive efforts to diagnose and treat this disorder in infants even more important.

GROWTH RETARDATION

Children with hereditary fructose intolerance learn by the age of 2 to avoid food containing fructose or substances which generate fructose in the gastrointestinal tract. They thereby avoid the severe acute and chronic symptoms experienced by infants with this biochemical disorder. It has now been found, however, that the ingestion by these children of amounts of fructose too small to produce symptoms can still produce a metabolic fructose intoxication which can lead to growth failure.

MENSTRUAL DYSFUNCTION

The major impact of physical exertion upon reproductive function in females has been indicated by a study of eight weeks of physical training of normally menstruating women. Ninety-two percent of the subjects exhibited changes in menstruation (irregular cycles, failure of menstruation) indicative of altered hormone patterns.

HEART FAILURE

A deficiency of carnitine, an amino acid which occurs naturally in skeletal muscle and liver, was the cause of a year-long congestive heart failure in a child with excessive urinary losses of this amino acid. Administration of carnitine cured the disorder. The results indicate that carnitine deficiency can present as cardiomyopathy rather than in the better-known way as skeletal muscle weakness; the frequency of this deficiency as a cause of heart symptoms needs to be determined.

Prevention

BLOOD CHOLESTEROL LEVELS

Contrary to popular belief, shellfish consumption does not significantly increase the level of cholesterol in the blood of most people. Shellfish contain much cholesterol, but apparently the uptake of this cholesterol is counteracted by the uptake of certain fatty acids also present in the shellfish but lacking in foods from other animals.

VITAMIN E DEFICIENCY

Cholestasis in children, a failure of bile flow usually caused by congenital abnormalities of bile ducts in the liver, often results in symptoms from deficiencies of the fat-soluble vitamins. Most recently described is a neurologic disorder associated with vitamin E deficiency, appearing before the age of 2. The clinical signs, involving failure of control of eye and skeletal muscles, are reversible if vitamin E repletion is initiated soon after they appear, but not later. This means that close surveillance of these patients for early signs of the deficiency is mandatory, coupled with aggressive efforts to prevent or reverse them.

Diagnosis and Prognosis

HAIR ANALYSIS

The chemical analysis of hair, extensively promoted by commercial laboratories as an aid to nutrition counseling, has been found to be worthless for the detection of vitamin deficiencies, and of very limited value in estimating the mineral status of the body. The dearth of information on how hair concentrations of nutrients correlate with body tissue levels, the lack of data on the normal range of trace element concentrations in hair, the contamination of hair with minerals from the environment, large variations in concentration with hair length, the effect of hair treatments, and differences in hair growth rate create technical problems which make data from hair analyses uninterpretable.

POST-TRANSFUSION SYNDROME

A newly discovered, short-lived, apparently benign post-transfusion syndrome causes a rash and blood abnormalities which mimic those in patients with the often-fatal graft-versus-host disease (GVHD). Physicians need to be alert for this disorder so that they do not conduct unnecessary, expensive diagnostic tests for GVHD, or prescribe possibly harmful treatments.

CARDIAC FUNCTION

Forceful coughing, repeated three times over a three-second period, may be useful in indicating a patient's capacity for cardioacceleration. Until now, routine measurements of this important indicator of heart function have been difficult to obtain, requiring the use of drugs or expensive and bulky equipment.

ALZHEIMER'S DISEASE

A surprisingly good predictive indicator for Alzheimer's disease has been identified. Among patients 75-85 years old with no evidence of dementia, less than 2 percent of those who made no errors on a simple, easily administered questionnaire called the Blessed Mental Status Score developed overt Alzheimer's disease within one year. Of those who made four to eight errors on the test, 20 percent developed Alzheimer's disease within one year.

DEAFNESS

Procedures have been developed for the diagnosis of perilymphatic fistula, a cause of sensorineural hearing loss and vertigo in children. Identification of this condition is important, because it is amenable to surgical correction.

CARCINOID SYNDROME

The carcinoid syndrome is a metabolic disturbance that occurs in patients who have liver metastases from intestinal carcinoids or have primary carcinoid tumors that drain into the vena cava system (such as bronchial carcinoids). The metabolic disturbance, which includes flushing of the skin, asthma, diarrhea, and right-sided valvular disease of the heart, is caused by tumor production of a variety of hormones and hormone-like substances. Infusion of pentagastrin elicits symptoms in all patients with liver metastases tested so far, providing an extremely reliable provocative test for the diagnosis of this syndrome.

THROMBOCYTOPENIA

A new assay of platelet survival which is based on inhibition of platelet enzyme activity is simple, safe, and convenient, requires a relatively small amount of blood, and does not involve radioisotope administration to the patient. It can be applied to a wider range of platelet-deficient patients than can radioisotope methods.

DIABETES INSIPIDUS

Diabetes insipidus is a disorder characterized by markedly abnormal increases in the intake and excretion of water. It can result from a deficiency of the antidiuretic hormone, insensitivity of the kidneys to the antidiuretic actions of the hormone (nephrogenic diabetes insipidus), or excessive drinking (polydipsia). Therapy must be tailored to the cause of the disorder, because measures which are effective and safe for one form of diabetes insipidus may produce fatal water intoxication if applied to another. GCRC-based investigators have demonstrated that standard diagnostic methods for differentiating among these three conditions are unreliable and can be improved considerably by incorporating direct assay of antidiuretic hormone. Use of this new diagnostic technique has now revealed that many patients previously thought to have nephrogenic diabetes insipidus secondary to therapy with the drug lithium carbonate actually have a drug-induced form of primary polydipsia. Recognition of this defect will significantly improve our ability to manage this troublesome complication of lithium, an effective and widely used drug for treating manic-depressive illness.

HYPERPARATHYROIDISM

A new assay which is specific for parathyroid hormone (PTH) and does not measure any of its metabolites circumvents problems of previous assays. With this new assay, a more reliable test for abnormalities in PTH secretion has been developed which involves titration of blood PTH levels against the simultaneously measured blood levels of ionized calcium. This technique has been used to detect excessive PTH secretion in patients with hyperparathyroidism with 100 percent reliability.

AMYLOIDOSIS

Aspiration of abdominal fat has been found to be highly reliable for the diagnosis of systemic amyloidosis. This should be the biopsy site of choice, because the technique is simpler to perform, lower in risk, and more likely to be diagnostic than biopsies from the usual sites (rectum, skin, kidney, bone marrow, liver). Handling of biopsy specimens is also easier, quicker, and more cost-effective than that of other kinds of biopsies.

Therapy

ATHEROSCLEROSIS

Glipizide, an investigational blood sugar-lowering drug used to treat non-insulin-dependent diabetes mellitus, also reduces blood levels of

triglycerides, cholesterol, and low-density lipoprotein-cholesterol, and increases high-density lipoprotein-cholesterol. These changes are all consistent with a decreased risk of atherosclerotic heart disease.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Thyrotropin-releasing hormone (TRH), which is present in spinal cord as well as brain and has several neurophysiologic effects on spinal cord function, was found to produce a transient improvement in muscle strength when administered subcutaneously or intravenously in large amounts to patients with the spinal degenerative disorder ALS. Two-hour infusions of the hormone directly into the space around the cord have produced definite though still temporary improvement in six of seven patients. Feasibility studies have shown that TRH can be administered through an indwelling catheter, and studies of long-term infusion are underway.

INTRAVENOUS GAMMA GLOBULIN

The results of one GCRC study of a gamma globulin suitable for intravenous use have been submitted to the Bureau of Biologics as part of an application for approval of this preparation. It can be given at more than three times the maximum dosage possible with the older, intramuscular material, and has been successfully used to halt or reverse the progression of chronic obstructive pulmonary disease in severely ill patients. Another center has established the efficacy, safety, and optimum dosage for intravenous gamma globulin therapy of antibody-deficiency syndromes. This is important because of the high cost of intravenous serum immunoglobulin and because doses above the optimum shorten its half-life.

Immune neutropenia of infancy has been found to respond well to intravenous gamma globulin therapy, as do refractory cases of immune hemolytic anemia, albeit to higher dosage. Side effects are generally minimal, and long-term benefits are achieved in at least some patients.

CHRONIC RENAL FAILURE

Efforts continue to improve the nutrition of patients with chronic renal failure. A regimen of protein restriction with added ketoacids has been found to arrest or significantly delay deterioration of renal function in the majority of patients with this condition.

CONGENITAL NEUTROPENIA

The antibiotic chloramphenicol has long been known to suppress immune function sometimes by causing neutropenia, a decrease in the number of white blood cells which protect the body against bacterial infection. A patient was found, however, in whom this drug had the opposite effect, reversing a life-threatening neutropenia by inducing maturation and release of neutrophils. The results indicate that chloramphenicol should be given a therapeutic trial in other patients with congenital neutropenia; indeed, the publication of this finding immediately led to successful treatment of another patient.

TOURETTE SYNDROME

The tranquilizer haloperidol relieves the compulsive behavior, vocal and facial tics, and other symptoms of the neuropsychiatric disorder called Tourette syndrome, but serious side effects can limit its use. It has now been learned that the antihypertensive drug clonidine is effective in a majority of Tourette patients, without serious side effects or problems of drug tolerance. In this same study, the investigators learned that multiple tics, a disorder involving a variety of compulsive movements, appears to be a mild form of the same disorder, indicating that the Tourette syndrome is more common than has been thought.

DIABETES

Thickening of the capillary basement membrane, one of the earliest complications of diabetes mellitus, can be reduced by two years of strict control of blood glucose levels with the insulin infusion pump. Use of these pumps has become very widespread, but there has been little previous evidence that they can control the vascular degeneration characteristic of the disease.

SICKLE CELL ANEMIA

Some patients with the delayed growth and maturation characteristic of sickle cell anemia can be treated successfully with the drug clomiphene citrate. The drug is effective in those patients whose pituitary glands are functioning normally but who have a defect in the production of gonadotropin-releasing hormone from the hypothalamus, a part of the brain.

GAUCHER'S DISEASE

The transplantation of normal bone marrow cells into a child with type III Gaucher's disease, a hereditary lipid storage disorder, successfully corrected the enzymatic abnormality in blood primary cells. Although the

patient later died of infection, the work provides hope of a new means of treating the progressive deterioration characteristic of this disorder.

FAMILIAL HYPERCHOLESTEROLEMIA

Children with homozygous familial hypercholesterolemia usually develop severe cardiovascular disease in the second decade of life and do not respond to most drug therapies aimed at lowering their elevated plasma cholesterol levels. One child with this disease was treated some years ago on a GCRC with a surgical procedure called portacaval anastamosis, which allows blood returning from the intestinal tract to bypass the liver, and responded dramatically. Studies now underway in six patients with this disorder show that portacaval anastamosis significantly reduces plasma low-density lipoprotein cholesterol levels in these patients and causes a dissolution of the cholesterol deposits in tendons and under the skin. The operation decreases both endogenous cholesterol synthesis and the total mass of exchangeable cholesterol in the body, and has thus far produced no detrimental effects on hepatic or neurologic function.

LARYNGEAL TUMORS

GCRCs have been extensively involved in a collaborative study of the use of interferon therapy to reduce the need for surgery in children with juvenile laryngeal papillomatosis. This troublesome, recurrent tumor of the vocal cords has been previously treated with laser and cryosurgery. Preliminary results indicate excellent success of this drug in producing total cure in some patients and reducing the number of operations needed in others.

FUNGUS DISEASES

Research protocols of the Mycosis Studies Group, a collaborative group supported by the National Institute of Allergy and Infectious Diseases, have utilized GCRC resources. These investigations have included studies which suggest that the newly introduced drug ketoconazole is very effective in the treatment of systemic fungal infections, particularly coccidioidomycosis. Facilities in one center have been important for the pharmacokinetic studies of ketoconazole concentrations in blood, spinal fluid, and other secretions essential for the testing of new dosage regimens.

CORONARY ARTERIOSCLEROSIS

The balloon catheterization method has been modified to make it effective and safe for re-opening completely obstructed coronary arteries, as well as

partially obstructed ones. The new procedure involves threading a flexible guide wire through the arterial block, slipping a balloon-tipped catheter over the guide, and inflating the balloon to break the obstruction.

A reduction in heart rate at rest and during exercise may be of major benefit in patients with occlusive coronary artery disease. A new pharmacologic method for suppressing the heart rate involves selective chronic stimulation of the beta chronotropic receptors.

KIDNEY STONES

Research conducted on a GCRC has resulted in FDA approval of potassium citrate as an important drug for the prevention of calcium-containing renal stones. Citrate acts by reducing crystallization of stone salts. In a long-term clinical trial, 77 percent of citrate-treated patients did not form more stones and 95 percent experienced a reduced stone formation rate.

EXTRACORPOREAL PHOTOPHERESIS

A new therapeutic modality for the management of disorders caused by abnormal lymphocytes, leukemic or autoimmune in nature, involves passage of blood containing a photo-activable compound from one arm vein through an ultraviolet exposure system and then back to the patient through another arm vein. In this manner, an otherwise pharmacologically inactive drug can be activated in the bloodstream to produce profound and desirable effects on circulating lymphocytes while sparing other body tissues. The procedure has been found safe in some circumstances and is undergoing clinical trials.

ABDOMINAL SURGERY

New surgical approaches have been developed for patients who require total removal of the large intestine for the treatment of severe colitis, familial multiple polyposis, and some cancers. Previously, patients have required an incontinent ileostomy. New approaches provide the patient with a continent rectal sphincter and do away with the need for an externally worn abdominal bag in which feces are collected.

OVARIAN CARCINOMA

Certain tumors which are sensitive to a therapeutic agent *in vitro* fail to respond to that agent *in vivo*, possibly because of inadequate delivery of drug to the tumor. An evaluation has begun of improving drug delivery to ovarian tumors by instilling cisplatin directly into the peritoneal cavity. This drug is one of the most effective available for ovarian carcinoma, but

its dosage is limited by kidney toxicity when it is administered intravenously. The observations made during these studies strongly suggest that intracavitary chemotherapy has significant advantages for the management of patients with ovarian carcinoma.

TESTICULAR CANCER

Investigators at a GCRC were the first to demonstrate that combination chemotherapy consisting of cisplatin, vinblastine, and bleomycin was able to induce a five-year survival in excess of 60 percent in patients with disseminated testicular cancer, a cure rate higher than with any previous method. Recent studies show that maintenance therapy is not necessary after initial complete remission of these cancers. They also provide evidence that testicular function, including sperm production, usually returns after chemotherapy.

HEMOCHROMATOSIS

A study of desferrioxamine for treatment of transfusional iron overload has shown that long-term administration of this agent can halt and sometimes reverse the accumulation of iron in the liver and slow the progress of pituitary and pancreatic dysfunction.

CYSTINOSIS

Nephropathic cystinosis is a lethal hereditary disorder which results in end-stage renal disease by the age of 10 as a result of tissue accumulation of cystine in the kidney. A multicenter clinical trial begun on a GCRC has demonstrated that chronic treatment of cystinosis patients with cysteamine helps mobilize cystine from their tissues, preserving kidney function and enhancing linear growth. Other promising agents, which do not have the unpleasant taste and smell of cysteamine, are also being tested.

WILSON'S DISEASE

Studies of zinc therapy in sickle cell disease revealed that oral zinc results in a change in the intestinal cells which strongly blocks copper uptake, leading ultimately to copper deficiency. This result suggested a trial of zinc therapy in patients with Wilson's disease, in which harmful amounts of copper accumulate in the liver, brain, cornea, and other organs; Wilson's disease is usually treated effectively with penicillamine, but this drug is toxic to many patients. Zinc as sole therapy is extremely effective in blocking copper absorption from food and reabsorption from saliva and

gastric secretions, puts patients into negative copper balance, and is effective as long-term therapy.

RED CELL APLASIA

Pure red cell aplasia is a rare disease in which patients become anemic because red cell precursors disappear from the marrow. Many studies from GCRCs and elsewhere have shown that this condition is caused by an antibody that attacks and destroys the marrow red cells. At one GCRC, the many forms of treatment which have been tried over the last ten years were restudied, and guidelines were established for therapy. Combining three different forms of treatment, corticosteroids, cyclophosphamide, and splenectomy, has produced a cure in 70 percent of these patients. In addition, an association between rheumatoid arthritis and antibody-induced red cell aplasia has been recognized; it may account for the anemia which occurs in almost half of the patients with rheumatoid arthritis. Finally, a form of red cell aplasia that develops in epileptic patients treated with dilantin has been found to result from a binding of the drug to marrow cells, changing them in such a way that they stimulate formation of a cell-destroying antibody.

OSTEODYSTROPHY

Accumulation of aluminum from oral medication and from the large volumes of water used in dialysis has been found to be a common cause of the bone softening often seen in chronic renal disease. A new non-invasive procedure to replace the bone biopsy previously necessary to diagnose aluminum accumulation involves the infusion of desferrioxamine, a substance which binds aluminum and removes it from the bone into the blood. Moreover, the long-term use of desferrioxamine is a promising therapy for this debilitating complication of renal failure.

INTRODUCTION

MISSION

The Minority Biomedical Research Support (MBRS) Program seeks to relieve the shortage of minority representation in biomedical research by strengthening institutional research capabilities and by promoting minority faculty and student research participation at eligible institutions. The MBRS initiatives are expected to produce minority scientists who will contribute significantly to the health sciences.

OBJECTIVES

The objective of the MBRS Program is to increase the number and quality of minority biomedical research scientists. The Program accomplishes its objectives by:

- strengthening the capability of eligible institutions to support the conduct of quality research in the health sciences;
- supporting faculty at eligible institutions as they initiate or expand their biomedical research interests and capabilities; and
- supporting minority students engaged in research projects at the undergraduate and graduate levels to motivate and prepare them for careers in biomedical research.

PROGRAM DESCRIPTION

BACKGROUND

The MBRS Program was established to respond to the severe under-representation of minorities in biomedical research.

In Fiscal Year 1972, under the authority of Section 301(c) (now 301(a)(3)) of the Public Health Service Act, as amended (42 U.S.C. 241(d)), the Division of Research Resources (DRR) initiated the Minority Schools Biomedical Support Program, later shortened to the Minority Biomedical Support Program. In 1982, it was renamed the Minority Biomedical Research

Support (MBRS) Program to emphasize its function as a research program. The program focuses on colleges, universities, and health professional schools in which 50 percent or more of the students are classified as minority. Other institutions, including those on American Indian reservations, with substantial minority enrollments (but less than 50 percent) that demonstrate special commitment and assistance to minority faculty and students also are eligible. The Program was expanded in 1975 to include two-year institutions.

Through release time, the MBRS Program provides funds that allow faculty with full-time teaching appointments the opportunity to engage in biomedical research. It supports equipment, supplies, and necessary renovations for approved research projects, and also provides funds for student participation in research. Faculty at institutions that grant Ph.D. degrees are encouraged to participate as associate investigators; MBRS funds allow minority students to become involved in biomedical research projects that are funded from other sources. In addition, the Program supports consortia, collaborative arrangements, and travel to scientific meetings.

GROWTH AND SCOPE OF THE PROGRAM

The Program made the first grant awards, totaling $2 million, to 38 institutions in 1972. By 1984, the number of grantees had increased to 81 and the appropriation for the Program had increased to $21.9 million.

The current grantee portfolio includes 4 two-year colleges and 34, 25, and 18 institutions which offer as their highest degree baccalaureate, masters, and doctorate degrees, respectively. The MBRS Program offers 4 grants that serve primarily American Indians, 47 that serve primarily blacks, 5 that serve primarily Puerto Ricans, and 2 that serve Hawaiians. The remainder serve a mixed population of minorities in large metropolitan areas and the Southwest. Five new MBRS Programs were started in 1984.

A new initiative implemented in 1983 to upgrade instrumentation at MBRS institutions has been continued; awards totaling $1.07 million were made to 15 of 37 applicants in 1984.

COFUNDING AND COST-SHARING WITH OTHER PROGRAMS

The MBRS Program established an administrative mechanism in Fiscal Year 1975 to involve other NIH institutes in funding some of the research projects at MBRS-supported institutions. The majority of the NIH Institutes, the National Institute of Alcohol Abuse and Alcoholism (NIAAA) and the National Institute of Mental Health (NIMH) in the Alcohol Drug Abuse and Mental Health Administration participate in these funding agreements with the MBRS Program. The arrangements permit cooperating institutes to pay the costs

for projects which are of direct concern to their stated missions and to assist the principal investigators in gaining individual research grant support from the categorical Institutes. The MBRS Program provides for the overall review and management of these projects, including budget negotiations and monitoring of progress and accomplishments. Table I illustrates the cofunding activity in Fiscal Year 1984.

Table I
Cofunding and Interagency Agreements Activity
FY 1984

Institute	Funds	No. of Projects
NCI	$3,133,697	56
NHLBI	2,347,939	46
NIAID	237,330	5
NIADDK	1,350,018	36
NIDR	38,524	1
NIA	193,391	5
NEI	272,232	10
NICHD	517,179	12
NINCDS	192,533	5
NIEHS	280,467	3
NIAAA	19,880	1
NIMH	1,350,000	26
GCRC (DRR)	165,925	-
TOTALS	$10,099,115	206

RESEARCH HIGHLIGHTS

In general, the quality and productivity of faculty and students participating in the MBRS Program have continued to improve. In Fiscal Year 1984, the Program supported positions for 1,020 undergraduate students, 388 graduate students, and 736 faculty. Research accomplishments were described in 777 scientific papers published by MBRS faculty and students and in 726 faculty and 879 student presentations at scientific meetings. For purposes of comparison, Figure I shows trends from 1974 to 1983.

INSTITUTIONAL DEVELOPMENT

Approximately 645 research projects were conducted at grantee institutions in Fiscal Year 1984, including 206 projects cofunded by ten NIH Institutes, NIAAA and NIMH. Areas of research ranged from clinical studies on hypertension to recombinant DNA technology. The diverse nature and sophistication of this research are in marked contrast to studies conducted during the early years of the MBRS Program. To bring about improvements, the program supported contemporary research equipment and other resources at grantee institutions; this attracted more research-oriented faculty, enhanced instructional capabilities in science laboratories, and aided recruitment of students.

Agreements with other DRR programs also have bolstered institutional research capability. The General Clinical Research Centers Program, DRR, cofunded a grant to Meharry Medical College to help develop a small clinical research center, and the Biomedical Research Technology Program, DRR, has provided funding and technical support to establish a PROPHET computer system at six MBRS institutions. This system manipulates, analyzes, and transmits research data.

Institutional research capability also was enhanced in 1984 by the continuation of a supplemental instrumentation grant program initiated in 1983. High priority was assigned to replacing and upgrading research equipment needs for MBRS grantees in 1982 to enable the faculty at MBRS institutions to compete more successfully for other research support. To date, 38 supplemental grants ranging from $25,000 to $135,000 have enabled MBRS grantees to obtain state-of-the-art instrumentation, including spectrophotometers, spectrometers, and ultracentrifuges, plus other basic equipment items.

Data obtained during a short-term evaluation study of the MBRS Program suggest that grantee institutions are becoming more successful in obtaining other research and training grant support. There have been marked increases in NIH and other Public Health Service (PHS) funding over two recent consecutive five-year periods of MBRS support (1973-77 and 1978-82, respectively), compared to the five years immediately preceding the inception of the program (1968-72). For example, the percentage of current grantees receiving other support increased from 54 percent in the baseline period to 81 percent in the first five-year period (1973-77) and to 94 percent in the most recent period (1978-82).

FACULTY AND STUDENT DEVELOPMENT

Approximately 7,600 minority students have participated in the MBRS Program since 1972. Of the nearly 5,000 students receiving baccalaureate degrees, more than 80 percent have entered graduate schools; medical, dental, and

other health professional schools; and other health-related careers. In 1984, more than 1,400 students participated directly in research activities and attended scientific meetings and symposia. Many students made scientific presentations at these meetings, and some co-authored research publications.

Fiscal Year 1983 data, the most recent available, indicate that of the 586 MBRS graduates, 21 were accepted to dental school, 143 were accepted to medical school, 191 were accepted to graduate school, and 135 planned to continue their education at other health institutions. Most of the students who did not pursue advanced studies are employed in the health field. (See Figure II.)

During the period 1974-82, ten MBRS-supported institutions reported in their progress reports that approximately 70 minority students received Ph.D. degrees while participating in MBRS-funded projects. They are currently engaged in biomedical research, at either the post-doctoral or faculty level.

Using the National Academy of Sciences (NAS) Survey of Doctoral Recipients, the Division has begun to analyze and to match the NAS records of Ph.D. recipients with the names of approximately 7,600 students supported by MBRS in the years 1974-82. The first reports show that 118 students who were supported by MBRS have received the Ph.D.; 116 of these Ph.D.s were in science and engineering fields. Of the 118 students:

- 47% received their Ph.D. from MBRS-supported minority institutions;
- 74% received MBRS support as graduate students only; and
- 19% received MBRS support as undergraduates only.

The latest year of MBRS support cited for those supported as undergraduates only was 1974 (8), 1975 (6), 1976 (4), 1977 (3), and 1978 (1). Thus, the median interval between the bachelor's and Ph.D. degree is 6.8 years for MBRS students. Similar studies are underway to identify MBRS-supported students who received M.D. degrees, PHS Training and Fellowship awards, and PHS research grants.

Student participation at some institutions has been particularly active. For example, at Catholic University of Puerto Rico, 193 undergraduates have participated in the MBRS Program. Of these, 153 have received baccalaureate degrees, mostly in chemistry (81) and biology (56). As of May 1984, 35 had entered medical school; 32, graduate school; 30 were employed as chemists; 20, as medical technologists. Sixteen have received the M.D. degree, 3 are dentists, and at least 9 have received Ph.D.s or are in Ph.D. programs.

In another example, the MBRS Program at Xavier University, predominantly an undergraduate college in New Orleans, exemplifies the impact which MBRS support has had on student development. The MBRS Program at Xavier began in 1972. The data available as of January 1, 1983 indicate that 244 students have participated in this MBRS Program. The graduates include 22 medical doctors, 7 dentists, 2 Ph.D.s, 1 doctor of optometry, and 19 medical

technologists. Additionally, 5 students were awarded the master's degree (this includes 1 M.S.W. and 2 M.B.A.s); 26 students are currently enrolled in graduate or medical school (18 M.D. aspirants; 2 D.D.S.; 5 Ph.D.; and 1 LL.D.).

MBRS faculty have continued to refine their research skills and increase their contributions to biomedical research. A total of 736 faculty members participated in 645 research projects in Fiscal Year 1984. As a result of MBRS Program faculty development efforts, 63 faculty investigators have been awarded regular NIH grants, and 26 have been nominated to NIH advisory and review committees, compared to only 3 in 1973. Examples of research accomplishments by MBRS faculty in Fiscal Year 1984 follow.

MODULATOR PROTEIN

At Bethune Cookman College, an undergraduate college in Daytona Beach, Florida, an MBRS researcher has isolated, purified, and partially characterized heat-stable modulator proteins from Escherichia coli, bovine brain, and sperm. The modulator protein from bovine brain, which is relatively small and acidic, has been shown to have regulatory effects on several types of protein kinases and phosphoprotein phosphatases. The E. coli phosphoprotein is a relatively large, acidic protein, and is a modulator of a variety of enzymes. This investigator has previously shown that the conversion of mammalian cyclic GMP-dependent protein kinases into modulator-dependent protein kinase occurs spontaneously in the absence of cyclic GMP or histone. Efforts are continuing to ascertain the pathophysiological roles of these stimulatory protein kinase modulators at the cellular, subcellular, and molecular levels. Because these types of enzymes are associated with prostate cancer and spermatogenesis, a better understanding of their specific roles has significant health implications.

RELAXIN HORMONE

The MBRS Program at the University of Hawaii provides an example of the use of the associate investigator mechanism to provide student support to principal investigators who are well established as independent competitive biomedical research scientists. This program provides support for undergraduate student positions. These students are provided a variety of research experiences using contemporary research protocols and instrumentation, allowing each student to become familiar with the research process that is being used by his or her faculty mentor as a specific research question is being pursued. A typical example of this type of MBRS student research experience at Hawaii involves the isolation, purification, and characterization of the hormone relaxin by one of the associate investigators at this university. Students become well versed in the methodology needed to isolate this hormone from ovaries that have been removed from pregnant animals. Working in this laboratory, students are able to understand the important role which relaxin plays in the rapid delivery of the fetus. They come to realize that, although their research deals with porcine relaxin, this same hormone (as is true for many other drugs obtained from animal sources) plays a very prominent role in accelerating physio-

logical processes in the human system. In the case of relaxin, it increases the rate of thinning of the cervix in women induced to labor, and thereby decreases the number of contractions necessary for the delivery and reduces the number of women needing a cesarean section.

INTRACELLULAR PROTEIN DEGRADATION

MBRS investigators at New Mexico State University have been studying how the bacterium Bacillus subtilis accomplishes and controls intracellular protein degradation at the molecular level. They have developed a special chemically defined growth and sporulation medium for B. subtilis which results in very high rates of intracellular protein degradation. In searching for a regulatory mechanism to explain this phenomenon, they have identified a protein inhibitor which has physical properties comparable to calmodulins. Calmodulins have previously been found in eukaryotic and gram-negative bacteria. The discovery of calmodulin in B. subtilis is a very significant finding, because it is believed to be the first time that calmodulin has been found in a gram-positive bacterium. An MBRS undergraduate student conducted the initial work which led to this discovery.

DIABETES

In research at the Florida A&M University College of Pharmacy, a pharmacology professor and his MBRS graduate student have found preliminary evidence which suggests that diabetes adversely affects the nervous system in rats by interfering with the production of two enzymes, acetylcholinesterase (AChE) and choline acetyltransferase (ChAT). Both of these enzymes regulate the action of acetylcholine, a neurotransmitter vital to the nervous system. AChE breaks down acetylcholine, whereas ChAT stimulates its production.

In rats with drug-induced diabetes, the investigators detected abnormal levels of these enzymes in the cerebellum, cerebral cortex, medulla oblongata, and other areas of the brain. Diabetes apparently stimulates the production of both enzymes as the animal system attempts to maintain a normal level of acetylcholine. However, after a few days, a balance between these two enzymes is no longer maintained; the acetylcholine level becomes exceptionally high.

Overproduction of the ChAT enzyme has been correlated with higher-than-normal levels of acetylcholine. In humans, studies have linked high levels of acetylcholine to depression, and investigators have reported a relationship between diabetes and depression. Other neurological disorders also occur commonly among long-term diabetics.

The long-range goal is to find a drug therapy that can reduce the production of the cholinergic (ChAT) enzyme and alleviate some of the adverse effects that diabetes has on the nervous system. If such a drug is discovered through this research in rats, it may eventually lead to clinical trials in humans.

MEETINGS, WORKSHOPS, AND CONFERENCES

ANNUAL MBRS SYMPOSIUM

About 1,500 student and faculty participants in the MBRS Program gathered in Washington, D.C. April 10-13, 1984, for the 12th Annual MBRS Symposium. The students presented 570 papers and poster displays. Both faculty and students engaged in workshops on electron microscopy and high-performance liquid chromatography.

The keynote speaker was Dr. William A. Sadler, Chief of the Reproductive Sciences Branch, Center for Population Research, National Institute of Child Health and Human Development. He is a graduate and former faculty member of Texas Southern University, an MBRS grantee. He spoke about gaining access to biomedical research grant programs in today's highly competitive arena. A highlight of his talk was his "Ten Rules of Access to the NIH Grant System." Because these rules were formulated from the perspective of the pursuit of regular NIH grants, they should facilitate the acquisition of regular NIH grants by faculty who are now being supported through the MBRS/DRR Program.

Mini-symposia and lectures on "Nutrition and Aging," "Hypertension," and "AIDS" also were well attended by interested students and faculty. The banquet speaker was Congressman Louis Stokes of Ohio, who traced the history and background of the MBRS Program.

MBRS PROGRAM DIRECTORS' MEETING

The annual MBRS Program Directors' Meeting was held March 8-10, 1984, at the National 4-H Center in Washington, D.C.

Key discussion topics at this year's meeting focused on how to improve grant applications and increase the probability of success, and on improved and alternative MBRS strategies for meeting Program needs and opportunities in the 1980s. Other important areas for discussion involved DRR perspectives on MBRS accomplishments and needs, human subject and animal welfare issues, training authority for the MBRS Program, and institutional grants management considerations. Updates on MBRS Program policies, Minority Access to Research Careers (MARC) Program activities, and plans for the 12th Annual MBRS Symposium were also provided.

Much of the meeting was devoted to discussion of four proposed MBRS initiatives, developed by staff in response to recommendations made at a National Advisory Research Resources Council MBRS Workgroup Retreat held in September 1983. These proposals would address identified needs for:

- research participation for faculty and students at undergraduate colleges;

- o faculty research career enrichment awards;
- o motivational biomedical research-oriented experiences for students at two-year colleges; and
- o thematic grants which would focus on specific research themes for MBRS institutions with developing graduate programs.

NARRC/MBRS WORK GROUP RETREAT

The Council MBRS Work Group, together with several General Research Support Review Committee members, program directors, and other representatives of the minority research community, met September 12-13, 1983, in Washington, D.C., to review Program goals, discuss policy and Program management issues, and develop recommendations for future directions for the MBRS Program. There was general agreement on Program goals, with retreat participants recommending that a number of new initiatives and new funding mechanisms be developed to meet the diverse needs of MBRS-eligible institutions, and that application guidelines, review criteria, and reporting requirements be improved.

The MBRS Program staff has vigorously pursued follow-up activities throughout the year. Application guidelines and instructions have been updated and clarified and are currently being field-tested. Two new Program initiatives have been developed: an MBRS Grant Program for Undergraduate Colleges, and an MBRS Thematic Grant Program. These programs were announced in the summer of 1984; applications are due February 1, 1985. The development of several other initiatives and revisions of other Program documents and reporting procedures are continuing.

SHORT-TERM MBRS PROGRAM EVALUATION

The contract with Triton, Inc., for a short-term evaluation of the Program, which began in September 1982, was completed in 1984. Three interim reports were submitted: 1) the evaluation team's understanding of the Program, 2) an assessment of what aspects should be addressed in a short-term evaluation, and 3) a proposed data collection strategy. A final report was submitted early in Fiscal Year 1984, incorporating the team's findings and making recommendations for measuring and improving Program effectiveness. Staff has developed a digest of the report's findings and recommendations and is using this information to improve Program management and evaluation activities.

GRANTSMANSHIP WORKSHOP

As an aid to implementation of the initiative developed for biomedical research participation at undergraduate colleges, the MBRS Program conducted a grantsmanship workshop in Atlanta, Georgia, September 27-28, 1984. The purpose was to describe and explain this new program with prospective applicants; 41 institutional officials representing 38 eligible undergraduate colleges attended the meeting. The workshop agenda included a discussion of the NIH peer review process, essential elements of a good grant application, and a detailed review of the specific instructions to be followed in developing an MBRS proposal in response to this initiative.

POLICY CHANGES

Interim policies adopted in June 1983 were implemented in 1984. They require presubmission peer review of MBRS subprojects by applicant institutions, limit the total number of subprojects to 25 or fewer, and limit the total dollar amount requested in an application to $2 million per year and grant awards to $1.5 million per year (including indirect costs).

FUTURE DIRECTIONS

The current DRR Five-Year Plan outlines needs, opportunities, goals, and planned activities for the MBRS Program in the mid-1980s. The major goals are:

- to expand activities that enhance institutional biomedical research capability in institutions that show need and promise;
- to promote collaborative initiatives with the MARC Program, with other NIH programs, and with other agencies;
- to expand research career enrichment opportunities for faculty; and
- to continue to encourage and motivate students to choose biomedical research careers.

The MBRS Program intends to maintain a level of 72 or more fully funded MBRS institutional programs.

SPECIFIC ACTIVITIES PLANNED FOR 1985

INSTRUMENTATION AWARDS

Instrumentation continues to be a high-priority need. MBRS institutions have developed research programs which require the acquisition of sophisti-

cated new instrumentation that can be shared and the replacement of obsolete existing equipment. The quality and capability of instrumentation will be factors in the effectiveness and productivity of MBRS researchers. Because instrumentation can enhance institutional research capability, this initiative was implemented in 1983 and continued in 1984. Up to $1 million has been designated for instrumentation in 1985.

INITIATIVE FOR UNDERGRADUATE COLLEGES

An initiative will be implemented in 1985 for biomedical research participation by undergraduate colleges that have substantial enrollments of minority students and are not currently funded by the MBRS Program.

Since the initiation of the MBRS Program in 1972, many small undergraduate institutions have had only limited success in competing for sustained MBRS support. A new mechanism is necessary for such institutions to become more involved in the effort to increase the number of minorities prepared to pursue biomedical research careers. It is well recognized that these institutions have played and continue to play a major role in educating a substantial number of minority undergraduates, as indicated by a recent report by the Educational Testing Service. For example, black colleges award 40 percent of the baccalaureate degrees received by black students, even though these colleges enroll only about 17 percent of all black college students throughout the country. Budgetary constraints and other factors, however, have prevented the use of institutional funds to develop and support the resources needed to encourage the conduct of scientific research at these colleges. Prohibitively high faculty teaching loads (16-20 contact hours/week) have adverse effects on faculty research productivity. Neither traditional research support mechanisms, nor the MBRS Program as currently operated has been effective in assisting faculty to initiate and maintain research programs in many of these institutions.

In 1985, up to $1 million will be available for support of research efforts at minority undergraduate colleges, and it is expected that up to ten awards can be made.

INITIATIVE FOR THEMATIC PROJECT GRANTS

The MBRS Thematic Project Grant is a new activity for 1985. It is intended to be responsive to significant changes which have occurred in some MBRS institutions since 1972. By now some of these institutions with developing graduate programs have acquired a critical mass of biomedical research faculty and expanded and updated research equipment and other biomedical research resources. They are now capable of developing greater faculty and

interdepartmental collaboration around specific research themes or disciplines. The Thematic Project Grant, a new type of MBRS award, is intended as another transitional step toward regular NIH grant support.

In 1985, up to $1 million will be available to fund MBRS Thematic Project Grant applications, and it is expected that three to six awards can be made.

OTHER PROPOSED ACTIVITIES

The Advisory Committee and Council have identified several areas of high priority that require specific action to carry out Program goals. The areas are listed below in order of priority.

BIOMEDICAL RESEARCH ANIMAL FACILITIES IMPROVEMENT

As the research capabilities of MBRS institutions expand, more adequate animal facilities are needed. Provisions for special requirements for feeding, handling, caging, ventilation, and meeting other laboratory environmental conditions are continually demanded. It is essential that MBRS grantees be able to meet all requirements for proper and humane housing of experimental animals.

FACULTY RESEARCH CAREER ENRICHMENT AWARDS

Relatively few faculty at MBRS-eligible institutions have been successful in competing for nontargeted research support; a large number of these faculty have had a low success ratio when competing for support in the MBRS renewal application. Thus, there is a need to develop a mechanism that will update and expand the faculty research capabilities at these institutions.

Many of these faculty members have had difficulty in staying abreast of recent advances in their field or with the current technology needed to conduct competitive research. Although the MARC Program provides training opportunities of one to three years for faculty at minority institutions, a program which provides for shorter-term research experiences and development of skills in research-intensive environments is needed. Faculty participants would be off-campus for up to one year. This short-term experience would allow them to upgrade their investigative skills and establish collaborative ties with scientists at major biomedical research institutions. Once these faculty return to their home institutions, they will need some research support to conduct pilot studies; these pilot

studies could serve as the basis for developing a competitive research application.

MOTIVATIONAL PROGRAM FOR STUDENTS AT TWO-YEAR COLLEGES

Two-year community colleges represent the most accessible type of higher education for American Indians, as well as for a large percentage of Hispanics and large numbers of blacks. Approximately 50 percent of minority college students are in two-year colleges.

A new program is needed to provide motivational experiences and exposure to biomedical research as a career option for these students, because the current MBRS Program does not effectively address the needs of community colleges or provide the motivational experiences needed by minority students enrolled in two-year institutions. Only a handful of these schools have successfully competed for MBRS funds, leaving this vast minority student pool largely untapped.

A program needs to be developed to focus on selecting those students who have potential for and/or interest in continuing their education beyond the two-year institution and motivating them toward careers in health-related fields.

PORTABLE FELLOWSHIPS FOR FORMER MBRS STUDENTS WITH BACCALAUREATE DEGREES

Many MBRS undergraduates are unable to obtain support to continue their research interests after graduation. Only one-third of MBRS students receiving bachelor's degrees each year go to graduate school because of:

- lack of graduate programs at their undergraduate institutions;
- limited research opportunities at their institutions;
- stiff competition for available funds at major research schools;
- inability to match research interests with laboratories that have graduate student support available; and
- little opportunity for support in health professions schools.

Portable fellowships would provide:

- much more flexibility in selecting a research area and more choices of institutional affiliation for those who go to graduate school;

- o the opportunity for those in health professions schools to maintain an interest in research and to work toward a clinical research career; and

- o expanded opportunities to obtain graduate research training for those who elect to discontinue advanced studies and work instead.

All of these efforts are important to achieve the MBRS goal of increasing the numbers and quality of minority biomedical scientists.

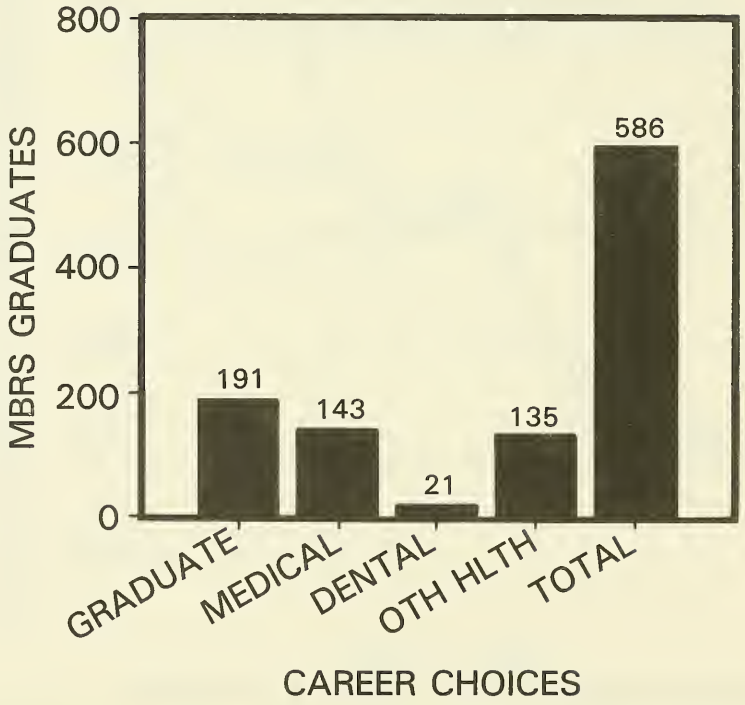
ADDITIONAL FIVE-YEAR PLAN ACTIVITIES

Student Initiatives

In many MBRS institutions, little opportunity exists for students to interact with researchers other than their mentors. Other factors that motivate students for biomedical research careers may be lacking because many MBRS institutions are isolated and small. Our limited experience in sending MBRS students off-campus during summers to NIH laboratories and other major universities has demonstrated that this is a most rewarding investment. To provide MBRS students with more opportunity for research exposure, summer research experiences are proposed. Salaries, as well as travel support, would be provided for students to spend a summer at a laboratory in a major research setting.

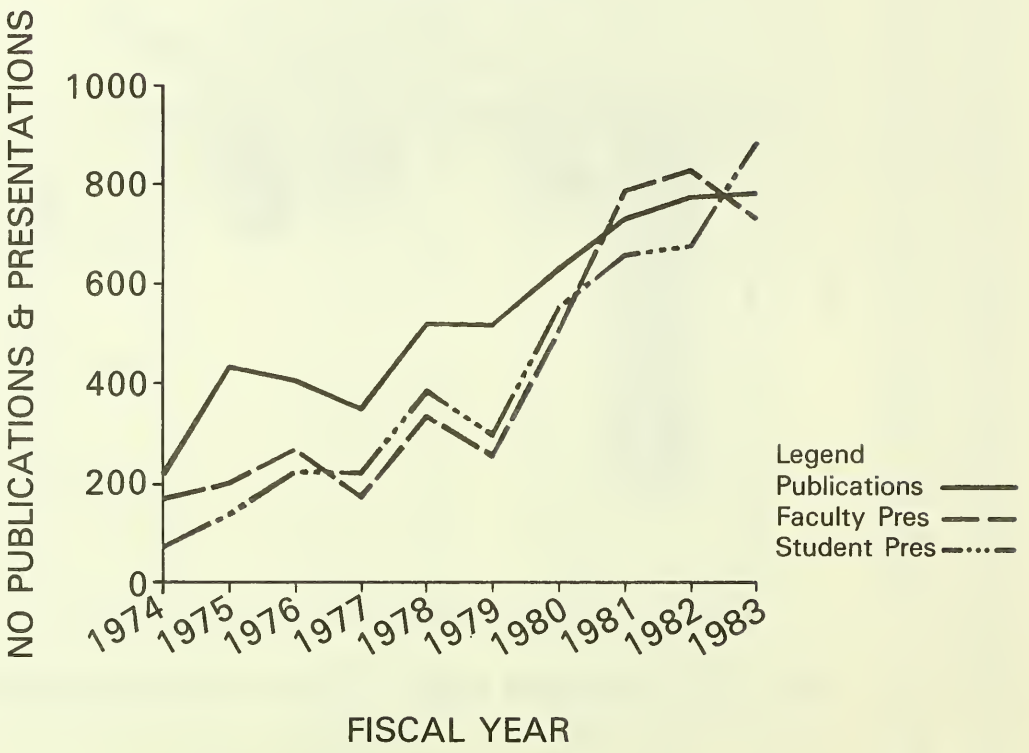
Over the years, the MBRS Program has graduated more than 2,000 students who have entered professional schools of medicine, dentistry, veterinary medicine, and other health professions. Many of these students continue their interest in research but find it difficult to obtain research support. The Program hopes to provide support for these students, on a pilot basis, to engage in research during their "off" quarters or summers. Eligibility would be based on previous MBRS participation, and payments would be made by the MBRS home institution.

CAREER CHOICES OF THE 1983 MBRS GRADUATES



Source: MBRS, DRR 11/84

MINORITY BIOMEDICAL RESEARCH SUPPORT PROGRAM
Research Publications and Presentations
1974 - 1983



Source: MBRS, DRR 11/84

NO. OF GRANTEES AND NO. OF PROJECTS FOR WHICH DATA ARE REPORTED EACH YEAR

YEAR	NO. OF PROJECTS	NO. OF GRANTEES
1974	314	63
1975	408	69
1976	378	75
1977	257	74
1978	318	71
1979	380	71
1980	488	79
1981	486	79
1982	521	78
1983	547	79
1984	645	81

SOURCE; MBRS, DRR 11/84

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